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Review

Ion channels in the regulation of apoptosis☆

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ABSTRACT

Apoptosis, a type of genetically controlled cell death, is a fundamental cellular mechanism utilized by multicellular organisms for disposal of cells that are no longer needed or potentially detrimental. Given the crucial role of apoptosis in physiology, deregulation of apoptotic machinery is associated with various diseases as well as abnormalities in development. Acquired resistance to apoptosis represents the common feature of most and perhaps all types of cancer. Therefore, repairing and reactivating apoptosis represents a promising strategy to fight cancer. Accumulated evidence identifies ion channels as essential regulators of apoptosis. However, the contribution of specific ion channels to apoptosis varies greatly depending on cell type, ion channel type and intracellular localization, pathology as well as intracellular signaling pathways involved. Here we discuss the involvement of major types of ion channels in apoptosis regulation. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Apoptosis, a type of genetically controlled or programmed cell death, is a fundamental cellular mechanism utilized by multicellular organisms for disposal of cells that are no longer needed or potentially detrimental [1]. Apoptosis is essential for normal tissue homeostasis and it is involved in cell turnover in many tissues. Further, apoptosis plays an important role in embryonic development, morphogenesis and shaping organisms [2]. Indeed, during embryonic development neuronal apoptosis sculpts the developing brain [3] whereas interdigital cell death contributes to digit individualization [4]. The role of apoptosis in termination of immune responses has also been reported [5,6]. Given the crucial role of apoptosis in physiology, it is not surprising that deregulation of apoptotic machinery is associated with various diseases as well as abnormalities in development. A number of pathological conditions, including cancer, viral infections and autoimmune diseases are characterized by apoptosis impairment, while other diseases, such as AIDS (acquired immunodeficiency syndrome), osteoporosis and neurodegenerative diseases involve increased apoptotic rate [7].

Accumulated evidence suggests that apoptosis plays an integral part in tumor development and progression [8]. Impairment in apoptosis

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breaks the balance between cell death and cell proliferation, leads to accumulation of "undead" cells and therefore supports cancerogenesis. Given that acquired resistance to apoptosis represents the common feature of most and perhaps all types of cancer, "evading apoptosis" has been defined by Hanahan and Weinberg as one of cancer hallmarks [9]. Resistance to apoptosis has been also implicated in moderate efficiency or failure of a number of anticancer treatments. Thus, targeting apoptosis represents a promising strategy to fight cancer [10,11].

Numerous studies suggest that by providing the influx/efflux of essential signaling ions, regulating cytoplasmic/intraorganellar ion concentrations, controlling cell volume, and maintaining membrane potential, ion channels are essential regulators of a number of fundamental cellular processes, including apoptosis [12–14]. Malignant transformation of cells, which is facilitated by apoptosis impairment, is often accompanied by alterations in ion channels' expression/function. Among these are both plasma membrane ion channels and intracellular ion channels, including potassium, calcium, sodium, and chloride channels, store-operated calcium channels, TRP (transient receptor potential) channels and others [15,16].

Here, we discuss the involvement of major types of ion channels in apoptosis regulatory pathways and the possible use of these channels in cancer treatment.

2. The apoptotic machinery

Apoptosis could be distinguished from other types of cell death by characteristic biochemical and morphological features including cell shrinkage, chromatin condensation, nuclear fragmentation, membrane blebbing and apoptotic bodies formation [1]. These bodies are subsequently phagocytosed by macrophages or neighboring cells. Importantly, as no cell leakage occurs during apoptosis, there is essentially no inflammatory reaction associated with this type of cell death in contrast to necrosis [17]. Thus, apoptosis represents a specialized tool for the body to focally and quietly eliminate unwanted cells with minimal if any bothering of nearby cells. It's clear that to achieve this result apoptosis should be tightly controlled at all stages, from initiation to final phagocytosis of apoptotic bodies.

The apoptotic machinery is highly complex and sophisticated, involving a variety of molecular players. Depending on the mechanism of initiation, signaling pathways that lead to apoptosis can be divided to two core pathways: the extrinsic (death receptor) pathway and the intrinsic (mitochondrial) pathway. However, it should be noted that despite the differences in mechanisms of initiation and molecules involved, these two pathways are closely interrelated [17,18]. Most of the morphological and biochemical changes observed in apoptotic cells are primarily caused by the activity of a family of cysteine proteases called caspases, which normally exist in healthy cells as inactive proenzymes and become activated upon apoptosis initiation [19]. Most of the known caspases have the role in apoptosis and can be divided into two groups: initiator caspases (e.g. caspase-8, caspase-9 and caspase-10) and effector caspases (e.g. caspase-3, caspase-6 and caspase-7). Initiator caspases activate effector caspases, which in turn realize much of the proteolisis and DNAses activation seen in apoptosis [19]. However, although pronounced caspase activation is frequently found in apoptosis, the cases of caspase-independent apoptosis have been reported as well [17,20].

As it goes from its name, intrinsic or mitochondrial pathway is initiated from within the cell and involves mitochondria as central regulators. The intrinsic pathway is highly regulated by the interactions between pro- and anti-apoptotic members of the B cell lymphoma 2 (BCL-2) family of proteins [21]. Stimuli that initiate this pathway include DNA damage, oxidative stress, unfolded proteins accumulation, cytosolic calcium overload and others. All of these stimuli induce changes in mitochondrial membranes permeability either through opening of mitochondrial permeability transition pore (MPTP) or through the pore-forming activity of pro-apoptotic members of the BCL-2 protein family, such as BCL-2-associated X protein (BAX) or BCL-2 antagonist or killer (BAK) [21–23]. The resulting mitochondrial outer membrane permeabilization (MOMP) causes loss of mitochondrial transmembrane potential ($\Delta\psi_m$), arrest of mitochondrial ATP synthesis and release of pro-apoptotic proteins from intermembrane space into the cytosol. These pro-apoptotic proteins include cytochrome c (Cyt C), second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI (SMAC/DIABLO), apoptosis-inducing factor (AIF), endonuclease G (EndoG), high-temperature requirement protein A2 (HTRA2/Omi) and others [24]. Cyt C, once released into the cytoplasm, forms apoptosome (by binding to apoptotic protease activating factor 1 (Apaf-1) and dATP) and triggers the activation of initiator caspase-9, which in turn activates effector caspase-3 [25]. HTRA2/Omi and SMAC/DIABLO antagonize inhibitors of apoptosis proteins (IAPs), thereby activating caspases (Fig. 1) [26,27]. In addition, HTRA2/Omi can induce caspase-independent apoptosis via its serine protease activity [28]. EndoG and AIF translocate to the nucleus, where they mediate caspase-independent DNA fragmentation [29,30].

Unlike intrinsic pathway, extrinsic pathway is induced by extracellular pro-apoptotic signals that activate specific surface receptors called death receptors (members of the tumor necrosis factor (TNF) receptor family) which in turn trigger apoptosis via caspase-dependent pathway [17,20,31]. Extracellular pro-apoptotic signals or ligands and their respective receptors include FAS/CD95 ligand—binds to CD95, TNFα—binds to TNFR1, TNF-related apoptosis inducing ligand (TRAIL)—binds to TRAILR1–2, and others [31]. Binding of ligands to death receptors initiates the formation of multiprotein complex dubbed death-inducing signaling complex (DISC), resulting in activation of initiator caspase-8 [32]. Active caspase 8 directly activates caspase-3, thereby triggering caspase-dependent apoptosis. Alternatively, caspase-8 mediates the cleavage of Bcl2-protein family member BH3-interacting domain death agonist (BID), resulting in a pro-apoptotic truncated BID (tBID), inducing subsequent MOMP, release of CytC from mitochondria and triggering caspase9-dependent apoptosis (Fig. 1) [33,34]. Of note, apart from death receptors, another receptor types, called dependence receptors, have been also demonstrated to mediate extrinsic apoptosis [35].

3. Ion channels in the regulation of cell apoptosis

Ion channels are integral membrane proteins that mediate the influx/efflux of essential signaling ions into/from the cell or intracellular organelles thereby controlling cytoplasmic/intraorganellar ion concentrations, membrane potential and cell volume. Numerous studies have demonstrated the involvement of different ion channels in the regulation of fundamental cellular processes, such as proliferation and apoptosis [12,13]. Among these channels are both plasma membrane- and intracellular ion channels, including potassium, calcium, sodium, and chloride channels, store-operated calcium channels, TRP (transient receptor potential) channels and others [15,16].

Further, we discuss specific roles of various ion channels in apoptosis in cancer, categorized by ion channel families.

3.1. Calcium and calcium-permeable channels

Calcium is a ubiquitous intracellular messenger playing a central role in many fundamental cellular processes such as cell proliferation, differentiation, gene transcription and cell death [36]. Numerous studies indicate that calcium is an important regulator of apoptosis at all stages, from initiation to final phagocytosis of apoptotic bodies [37,38]. Cytoplasmic calcium overload has been shown to promote apoptosis via different pathways. For example, excessive elevation of calcium in the cytosol stimulates increase in mitochondrial calcium uptake, which in turn can induce opening of MPTP resulting in triggering of intrinsic apoptotic pathway [24,39,40]. Another mechanism involves Ca^{2+}-dependent cysteine proteases, called calpains, which mediate cleavage

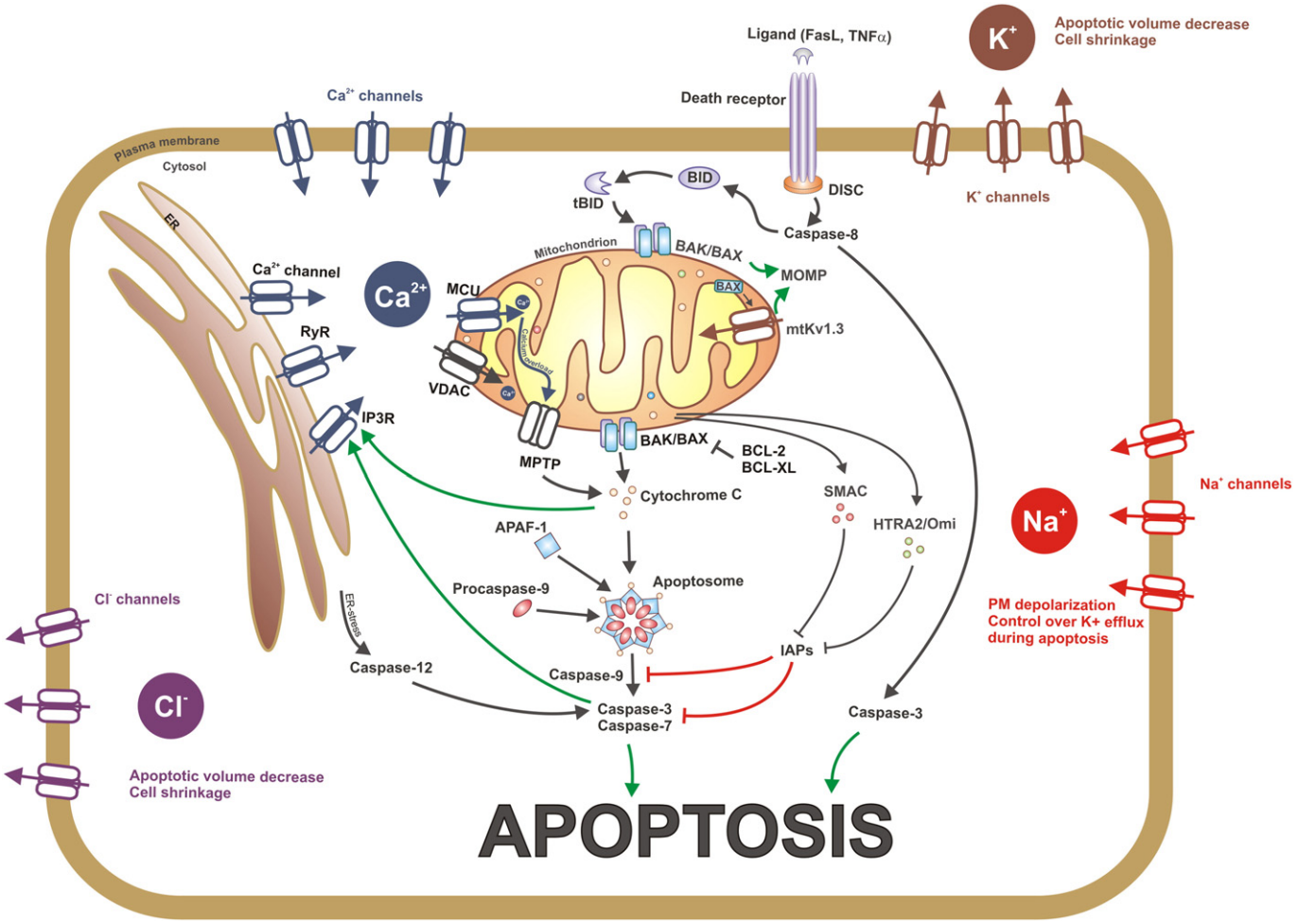

Fig. 1. Ions and ion channels in the regulation of apoptosis. Extrinsic and intrinsic apoptotic pathways are represented. Intrinsic pathway is initiated from within the cell following DNA damage, ER stress etc. These stimuli induce changes in mitochondrial membranes permeability which causes the release of proapoptotic factors from the intermembrane space. These pro-apoptotic proteins include cytochrome c (Cyt C), second mitochondria-derived activator of caspases/direct IAP-binding protein with low pl (SMAC/DIABLO), high-temperature requirement protein A2 (HTRA2/Omi) and others. Cyt C, once released into the cytoplasm, forms apoptosome (by binding to apoptotic protease activating factor 1 (Apaf-1) and dATP) and triggers the activation of initiator caspase-9, which in turn activates effector caspase-3. HTRA2/Omi and SMAC/DIABLO antagonize inhibitors of apoptosis proteins (IAPs), thereby activating caspases. Extrinsic pathway is induced by extracellular pro-apoptotic signals or ligands that activate death receptors which in turn trigger apoptosis via caspase-dependent pathway. Binding of ligands to death receptors initiates the formation of multiprotein complex dubbed death-inducing signaling complex (DISC), resulting in activation of initiator caspase-8. Active caspase 8 directly activates caspase-3, thereby triggering caspase-dependent apoptosis. Alternatively, caspase-8 mediates the cleavage of Bcl2-protein family member BH3-interacting domain death agonist (BID), resulting in a pro-apoptotic truncated BID (tBID), inducing subsequent MOMP, release of CytC from mitochondria and triggering caspase9-dependent apoptosis. Major types of ion channels involved in apoptosis regulation are represented.

of several members of BCL-2 family (including pro-apoptotic BID, as well as anti-apoptotic BCL-2 and BCL-2-like protein 1 (BCL-XL)), and promote MOMP and Cyt C release [41,42]. Cytosolic calcium overload (following treatment with calcium-mobilizing agents: ionomycin, A23187 or thapsigargin (TG)) has been also connected to apoptosis through the activation of Ca^{2+}-activated protein phosphatase calcineurin. Calcineurin dephosphorylates BCL-2-associated agonist of cell death (BAD), a pro-apoptotic member of the BCL-2 family, thus enhancing BAD heterodimerization with BCL-XL and promoting apoptosis [43].

Alternatively, ER-stress induction following alterations in ER-calcium homeostasis can activate specific ER-localized caspase-12 and thus can trigger apoptosis in a mitochondria-independent manner [44,45]. In addition, calcium-dependent cleavage and activation of caspase-12 by m-calpain has been suggested as a mechanism underlying apoptotic cell death induced by oxygen and glucose deprivation [46]. Increase in cytosolic calcium has been also connected to the activation of several DNA-degrading endonucleases [47].

Mitochondrial, ER and cytosolic calcium levels are regulated by calcium permeable ion channels localized either on the membranes of specific intracellular organelles or on the plasma membrane [48,49]. These calcium permeable channels are highly heterogenous and include families of transient receptor potential (TRP) channels, store-operated channels (SOCs), voltage-gated calcium channels, as well as mitochondrial calcium uniporter (MCU), voltage-dependent anion channels (VDACs), IP_3 and ryanodine receptors, and others. These channels contribute to changes in $[Ca^{2+}]_i$ by providing Ca^{2+} entry pathways, by modulating the driving force for the Ca^{2+} entry, and also by providing intracellular pathways for Ca^{2+} uptake/release into/from cellular organelles [48–51]. Thus, modulation of calcium-permeable ion channel's expression/function affects intracellular Ca^{2+} concentrations and consequently calcium-dependent processes, including apoptosis [10].

Inositol 1,4,5-trisphosphate receptor. The ER is the major Ca^{2+} store in most cells. The inositol 1,4,5-trisphosphate receptor (IP_3R) represents primary calcium release channel on ER membranes. Under normal conditions this channel is responsible for Ca^{2+} release into the cytoplasm, in response to inositol 1,4,5-trisphosphate ($InsP_3$) generation stimulated by numerous stimuli, to maintain normal calcium homeostasis [52,53]. Apoptotic stimuli often provoke increased calcium release through IP_3R, which in turn causes augmented mitochondrial calcium uptake and apoptosis induction [53]. In line with this silencing

of different IP_3R isoforms significantly diminished apoptosis in lymphocytes in response to different stimuli [54–56]. Several mechanisms underlying a pro-apoptotic role of IP_3R have been proposed. First, is direct transfer of calcium from ER to mitochondria through IP_3R [57]. Indeed, it is well established that ER and mitochondria form contacts, called mitochondria-associated membranes (MAMs), which are crucial for lipid and calcium exchange between these organelles [58]. IP_3R has been shown to localize to MAMs and mediate the calcium transfer from ER to mitochondria to support bioenergetics [59–61]. Stimulation of increased ER calcium release through IP_3R by apoptotic stimuli will enhance calcium uptake by nearby mitochondria, which may trigger apoptosis through opening of MPTP [40]. Second, is cleavage of IP_3R by caspase-3 or calpains, which has been suggested to provide an enhanced ER calcium leak pathway promoting cell death [62–65]. Third, is direct binding of Cyt C to IP_3R, which amplifies calcium-dependent apoptosis. It has been demonstrated, that in HeLa and PC12 cells treated with staurosporine Cyt C directly binds to IP_3R early in apoptosis and blocks Ca^{2+}-dependent inhibition of channel function, thus prolonging cytosolic Ca^{2+} oscillations and promoting further Cyt C release in a feed-forward loop [66]. Other mechanisms underlying a pro-apoptotic role of IP_3R include interaction with different members of BCL-2-family [67], phosphorylation by PKB/Akt, which leads to the suppression of "deadly" IP_3R activity and thus protects from apoptosis [68], pro-apoptotic regulation by phosphatase and tensin homolog deleted on chromosome 10 (PTEN) [69], pro-apoptotic modulation by the tumor suppressor promyelocytic leukemia protein (PML) [70], and others [67]. In cancer, current evidence suggests the importance of IP_3R in control of tumor growth, resistance to chemotherapy and aggressiveness. Thus, the anti-apoptotic role for IP_3R type III has been proposed in colorectal carcinoma, where knockdown of this receptor enhanced apoptosis, whereas high levels of IP_3R type III have been associated with increased aggressiveness [71]. The increased levels of IP_3R type III have been also found in glioblastoma cells [72]. In contrast, markedly reduced expression of IP_3R type I in cisplatin-resistant bladder cancer cells compared to parental cells has been demonstrated. Further, knockdown of IP_3R type I in these cells prevented cisplatin-induced apoptosis [73]. It seems that the contribution of IP_3R to cancer-related processes could vary depending on cancer type, IP_3 isoform involved, expression levels as well as regulation by proto-oncogenes and tumor suppressors [67].

Ryanodine receptor. The role of another major ER Ca^{2+}-release channel, ryanodine receptor (RyR), in the regulation of apoptosis is much less studied compared to IP_3R. It has been demonstrated, that RyR type II is involved in Ca^{2+}-transfer from sarcoplasmic reticulum (SR) to mitochondria in the heart through direct coupling of mitochondrial voltage-dependent anion channel 2 (VDAC2) with RyR type II [74]. Hence, apparently RyR could regulate apoptosis via similar to IP_3R pathways including opening of MPTP (following increased mitochondrial calcium uptake), activation of calcium-dependent effectors involved in the control of apoptosis (i.e. calpains) and others [75,76]. The involvement of RyR in TNFα-induced apoptosis in hepatoma cells has been also suggested [77]. Activity of both IP_3R and RyR has been shown to regulate the susceptibility of β-cells to ER stress resulting from impaired sarco/endoplasmic reticulum ATPase (SERCA) function [78]. Consistent with this, inhibition of ER Ca^{2+}-release through RyR and IP_3R has been demonstrated to protect cortical neurons against NMDA-induced excitotoxicity by reducing cytosolic Ca^{2+} increase and attenuating both mitochondrial damage and ER stress [79]. Recently, an anti-apoptotic BCL-2 protein has been identified as a new inhibitor of RyR suggesting an important regulatory mechanism, by which RyR activity controls cell fate [80].

Mitochondrial Calcium Uniporter. As it was stated above, the excessive mitochondrial calcium uptake can lead to the opening of MPTP resulting in triggering of intrinsic apoptotic pathway. Mitochondrial Calcium Uniporter (MCU) represents the calcium-permeable channel of the inner mitochondrial membrane responsible for Ca^{2+} uptake into the matrix and thus plays a crucial role in the control of metabolism and apoptosis [81,82]. Recent data have shown that microRNA miR-25 decreases mitochondrial Ca^{2+} uptake through selective MCU downregulation and in this way protects cells from Ca^{2+}-dependent apoptosis. MCU appears to be downregulated in human colon and prostate cancers and this correlates well with upregulation of miR-25 [83]. Expression of anti-miR-25 in PC3 prostate cancer cells or in HCT116 colon cancer cells increased mitochondrial Ca^{2+} levels and re-sensitized cells to apoptosis, confirming the key role of mitochondrial Ca^{2+} accumulation in the mitochondria-dependent apoptotic pathways [83]. In contrast, elevated levels of MCU have been detected in estrogen receptor negative and basal-like breast cancers [84]. Interestingly, MCU silencing did not alter caspase-dependent cell death initiated by BCL-2 inhibitor ABT-263, while ionomycin-induced caspase-independent cell death was potentiated by MCU knockdown independently of changes in cytosolic Ca^{2+} levels. Thus, the authors concluded that MCU overexpression may offer a survival advantage against some cell death pathways and inhibition of MCU was proposed as a therapeutic strategy to treat breast cancers [84]. Recently, the physiological role of mitochondrial calcium has been revealed by mice lacking the MCU [85]. Importantly, mitochondria from MCU(−/−) mice lacked evidence for calcium-induced MPTP opening. However, the lack of MPTP opening does not protect them against a wide range of apoptotic stimuli, indicating that, at least in some cell types, the uptake of calcium by mitochondria is not essential for apoptosis [85,86]. As for MPTP, several recent studies suggested that ATP synthase has a central role in mitochondrial permeability transition. Both ATP synthase dimmers as well as c-subunit of ATP synthase have been proposed to be the pore-forming units of MPTP [87–89]. Depletion of the c-subunit has been reported to inhibit Ca^{2+}- and H_2O_2-induced cell death to a similar extent to that of MPTP inhibitor cyclosporine A whereas increasing the expression of the c-subunit sensitized cells to death [87].

Voltage-dependent anion channel. Like MCU transfers Ca^{2+} across the inner mitochondrial membrane, the voltage-dependent anion channel (VDAC) imports Ca^{2+} across outer mitochondrial membrane (OMM). VDAC represents the most abundant protein of the OMM and its physiological function consists in transporting of ions, adenine nucleotides, NADH, and other metabolites between the cytoplasm and mitochondria [90]. VDAC has been proposed to mediate mitochondria-dependent cell death through the formation of MPTP [91], however this idea was challenged by other scientists [92]. Nevertheless, a number of studies strongly suggest that VDAC is critically involved in the regulation of cell fate through the interactions with numerous proteins including members of BCL-2 family, cytoskeletal elements, chaperones and others [57,93]. The final contribution of VDAC to cell death/survival has been also reported to be isoform- and stimulus-dependent. For example, VDAC1 is considered to be a pro-apoptotic protein [94], whereas VDAC2 has shown anti-apoptotic functions [95]. Interestingly, VDAC has been shown to have a higher permeability to Ca^{2+} in the closed state (associated with lower permeability to metabolites, disruption of mitochondrial homeostasis and apoptosis induction) than that in the open state [96,97]. Recombinant expression of VDAC has been reported to enhance the transfer of Ca^{2+} to mitochondria and increase the ceramide-induced cell death in HeLa cells [98]. Moreover, VDAC1 was shown to be physically linked to the IP_3R on ER through the molecular chaperone glucose-regulated protein 75 (GRP75), thus providing a direct pathway for Ca^{2+} transfer from ER to mitochondria [99]. In contrast, VDAC2 and VDAC3 isoforms do not form complexes with IP_3R, suggesting that anti-apoptotic role of VDAC2 does not involve the transmission of Ca^{2+} signals [100]. Thus, VDAC1 has been suggested to selectively transfer apoptotic Ca^{2+} signals to mitochondria [100].

Store-operated calcium channels. The store-operated calcium channels (SOCs) represent one of the major calcium-entry pathways in non-excitable cells. SOCs are plasma membrane ion channels activated in response to ER Ca^{2+} store depletion and thereby provide Ca^{2+} for ER store refilling as well as for signalling purposes [101]. The major molecular components of SOC are stromal interaction molecule 1 (STIM)

and ORAI1 proteins, where ORAI1 constitutes plasma membrane calcium channel and STIM1 represents an ER-localized protein, functioning as a sensor of ER calcium. Following ER Ca^{2+} depletion STIM1 translocates to the plasma membrane, where it interacts with and activates ORAI1 channel, thereby mediating store-operated calcium entry (SOCE) [102,103]. SOCs and in particular their major components ORAI1 and STIM1 have been shown to be implicated in a number of physiological and pathological processes including apoptosis [104,105]. However, the role of SOCs in apoptosis seems to be dependent on multiple factors such as cell type, apoptotic stimuli as well as intracellular signaling pathway involved. Thus, several studies suggest that SOCE, ORAI1 as well as STIM1 contribute to apoptosis induced by various stress stimuli [106,107], whereas others demonstrate their pro-survival antiapoptotic role [108–111]. Indeed, ORAI1 has been demonstrated to contribute to the establishment of an apoptosis-resistant phenotype in prostate cancer cells and ORAI1 knockdown protected LNCaP cells against TG- or oxaliplatin/cisplatin-induced apoptosis [106]. The authors proposed that ORAI1 constitutes the principal source of Ca^{2+} influx used by prostate cancer cells to trigger apoptosis via mitochondrial and cytosolic mechanisms [106]. Consistent with this, pharmacological SOCE inhibition or STIM1 knockdown have been shown to inhibit hydrogen peroxide-induced apoptosis in HT22 cells via alleviation of intracellular Ca^{2+} overload, restoration of the mitochondrial membrane potential and decrease of cytochrome C release [112]. In contrast, pharmacological inhibition of SOCE or downregulation of STIM1 have been shown to enhance apoptosis induced by cisplatin in non-small cell lung cancer cells [110]. Similar results were obtained on ovary carcinoma cells, where cisplatin-induced apoptosis was significantly lower in cisplatin-resistant cells (characterized by the increased expression of both ORAI1 and STIM1) than in parental cells. Pharmacological SOC inhibition by 2-APB or Akt inhibition by SH-6 restored cisplatin sensitivity of resistant cells. The authors concluded, that ORAI1/STIM1 play protective anti-apoptotic role in these cells and proposed that enhanced Akt activity could be responsible for this [113]. Recently, we have demonstrated that ORAI1 and STIM1 play pro-survival antiapoptotic role in pancreatic adenocarcinoma cell lines, as siRNA mediated knockdown of ORAI1 and/or STIM1 increased apoptosis induced by chemotherapy drugs 5-fluorouracil (5-FU) or gemcitabine [109]. Further, it was reported that Orai1-driven Ca^{2+}-entry delays the induction of the CD95-mediated apoptotic signal in leukemic T-cell lines through the translocation of the Ca^{2+}-dependent protein kinase C (PKC) β2 to the DISC and its subsequent inactivation in T-cells. This prevented CD95-mediated caspase activation and delayed delivery of the apoptotic signal [108]. When analyzing the involvement of SOCs in apoptosis regulation in different cell models, one should take in mind that ORAI protein family comprises three members ORAI1, ORAI2 and ORAI3, whereas STIM family is represented by two isoforms STIM1 and STIM2. All of these proteins participate in SOCE in different ways as well as have SOCE-independent functions [114,115]. Therefore, future research is indispensable to better understand the specific mechanisms of apoptosis regulation by SOCE to finally conclude if their modulators could be effective in cancer treatment in each particular case.

Transient receptor potential channels. Transient receptor potential channels (TRP) channels are a large superfamily of 28 mammalian cation channels with diverse physiological functions and cellular distributions [51]. This superfamily is divided into six subfamilies (TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin-like), TRPP (polycystin), TRPML (mucolipin)) based on structural homology. Most of TRPs are non-selective Ca^{2+}-permeable cation channels, with the exception of TRPM4 and TRPM5, which are not permeable for Ca^{2+}. The members of TRP family are activated by a plethora of different stimuli (including temperature changes, mechanical force, extra- and intracellular messengers, osmotic stress and many others) and function as important regulators of various cellular processes [51]. Consequently, defects in expression/function of these channels have been linked to human diseases [116]. Current evidence supports that TRP channels are implicated in the regulation of cellular processes altered in cancer, including proliferation, differentiation, migration and apoptosis [117]. Hereafter we discuss the involvement of some TRPs in the regulation of apoptosis.

TRPM2, a widely expressed ion channel-enzyme, contains an enzymatic region with ADP-ribose (ADPR)-hydrolase activity [118]. It has been proposed that the main physiological role of TRPM2 is to control cytokine release in human monocytes [119]. TRPM2 knockdown in rat insulinoma RIN-5 F cells has been demonstrated to significantly suppress Ca^{2+} influx and cell death induced by H_2O_2 and TNFα, whereas the heterologous overexpression of this channel enhanced H_2O_2-induced apoptosis [120]. In malignant melanoma and prostate cancer TRPM2 function has been shown to be downregulated due to the upregulation of antisense TRPM2 transcripts. Functional knockdown of these antisense transcripts or over-expression of wild-type TRPM2 increases melanoma and prostate cancer cells susceptibility to apoptosis [121,122].

TRPM7, another ubiquitously expressed Ca^{2+}-permeable nonselective cation channel with enzyme activity, contains an atypical serine/threonine protein kinase within the C-terminal domain [123]. It is involved in the regulation of cellular magnesium homeostasis [124]. In rat basophilic leukemia mast cell line RBL-2H3 siRNA-mediated knockdown of TRPM7 has been reported to significantly increase apoptotic cell death [125]. The crucial importance of TRPM7 for cell survival has been suggested for mast cells [126], lymphocytes [127], gastric adenocarcinoma cells [128]. In contrast, TRPM7 has been shown to positively regulate Fas-induced apoptosis in T-lymphocytes [129]. The authors suggested that in response to Fas-signaling in the early phase of apoptosis, TRPM7 undergoes a caspase-mediated cleavage to generate two distinct proteins, the TRPM7 channel and the TRPM7 kinase. The cleaved channel potentiates Fas-induced apoptosis through the maintenance of Fas receptor internalization following receptor stimulation. Knockdown of TRPM7 impaired the Fas receptor internalization thus mediating the reduction in their sensitivity to Fas-induced apoptosis [129].

TRPM8, a cold receptor in sensory neurons [130,131], was first cloned from the human prostate as prostate-specific gene upregulated in cancer [132]. TRPM8 has been proposed to form a calcium-permeable channel at both plasma membrane and ER membranes in prostate cancer cells [133,134]. TRPM8 has been suggested to be required for the survival of prostate cancer cells, as pharmacological inhibition by capsazepine or knockdown of TRPM8 in prostate cancer LNCaP cells induced apoptosis [135]. However, in the same experimental conditions, activation of TRPM8 by menthol also induced apoptosis in LNCaP cells [135]. The authors concluded that the normal function of TRPM8 is required for LNCaP cell survival, whereas menthol-induced cell death is mediated at least in part by the sustained increase in cytosolic calcium [135]. In line with this, TRPM8 activation by menthol was reported to decrease the viability of melanoma cells, presumably by calcium-dependent mechanism [136]. Further, in human bladder cancer cells menthol induces cell death via TRPM8-mediated mitochondrial membrane depolarization [137]. Consistent with this, menthol has been demonstrated to induce TRPM8-mediated apoptosis in rat synoviocytes via mitochondrial membrane depolarization and caspases activation [138]. In contrast, knockdown of TRPM8 has been reported to enhance epirubicin-induced apoptosis in human osteosarcoma cells [139].

Several members of the vanilloid subfamily of TRP channels have been also implicated in the regulation of apoptosis. TRPV1 was originally identified in sensory neurons as a heat-activated ion channel, which functions as a transducer of painful thermal stimuli in vivo [140]. The tumor suppressor function has been suggested for TRPV1, as its expression inversely correlates with tumor grade and growth in many cancers [141–143]. Capsaicin, the TRPV1 agonist, has been reported to induce TRPV1-dependent apoptosis in glioma cells. The authors demonstrated that capsaicin induced TRPV1-mediated Ca^{2+} influx, p38 mitogen-activated protein kinase activation, phosphatidylserine exposure, mitochondrial permeability transition pore opening and mitochondrial transmembrane potential dissipation as well as caspase-3 activation

[141]. In urothelial cancer cells activation of TRPV1 by capsaicin has been suggested to induce apoptosis by both extrinsic Fas/CD95-dependent and intrinsic mitochondrial pathway [144]. Recently, synthetic vanilloid arvanil was proposed as therapeutics for high-grade astrocytoma [145]. By activating the ER-localized TRPV1 channel, which is significantly overexpressed in this type of cancer cells, it induces ER-stress thereby promoting tumor cell apoptosis [145]. TRPV1-mediated apoptotic cell death in rat cortical cultures has been reported to be dependent on L-type Ca^{2+} channel opening, Ca^{2+} influx, ERK phosphorylation, and reactive oxygen species production [146]. However, it should be noted that capsaicin as well as other vanilloids have been shown to affect apoptosis independently of TRPV1. For example, in human small cell lung cancer capsaicin induces apoptosis via the TRPV6 channel and the calpain pathway [147]. The role for TRPV6 in capsaicin-induced apoptosis was also confirmed in gastric cancer cells [148]. Also, several vanilloids have been proposed to act as mitochondrial inhibitors, able to activate apoptosis and/or necrosis via non-receptor mediated mechanisms [149].

TRPV2, another heat-activated TRPV channel, has been reported to be overexpressed in several cancers [150,151]. In glioma cells, TRPV2 knockdown increased cell survival via ERK-dependent increase in BCL-XL expression, Akt/PKB phosphorylation and decrease in Fas expression [152]. Accordingly, TRPV2 overexpression increased spontaneous apoptosis and sensitised glioma cells to Fas- and chemotherapy-induced apoptosis [152]. Further, triggering of the TRPV2 by cannabidiol was demonstrated to sensitize glioblastoma cells to chemotherapy-induced apoptosis [153]. Activation of TRPV2 by cannabidiol has been also linked to apoptotic cell death in human T24 bladder cancer cells. It has been proposed that T24 cell death occurred via apoptosis caused by continuous influx of calcium through TRPV2 [154]. In prostate cancer, TRPV2 has been suggested to contribute to apoptotic resistance of androgen-independent prostate cancer cell lines, likely by augmenting Ca^{2+} influx into these cells [155].

TRPV6, a channel mediating intestinal calcium absorption in duodendum, has been also found to be overexpressed in many cancers [156,157]. In prostate cancer TRPV6 expression correlates with tumor grade and TRPV6-mediated Ca^{2+} entry has been suggested to be involved in apoptosis resistance of LNCaP cells [158]. An elevated expression of TRPV6 was also detected in colon carcinoma cells, where siRNA-mediated TRPV6 knockdown inhibited proliferation and induced apoptosis [159].

The members of TRPC subfamily also contribute to apoptosis regulation. For example, TRPC6 overexpression induces calcium-dependent apoptosis in cancer cells [160]. TRPC6-mediated calcium entry has been demonstrated to be involved in high glucose-induced podocyte apoptosis through the RhoA/ROCK pathway [161].

TRPC1-mediated Ca^{2+} influx has been implicated in oxidized low-density lipoprotein-induced apoptosis in vascular smooth muscle cells [162]. Further, TRPC1 overexpression has been found to sensitize intestinal epithelial cells to apoptosis by increasing activity of protein phosphatase 2A followed by the NF-kappaB inhibition [163]. In contrast, TRPC1 was shown to protect human neuroblastoma cells against salsolinol-induced apoptosis by inhibiting cytochrome c release and BAX downregulation [164].

Other subfamilies of TRP family also have their representatives in apoptosis regulatory pathways. TRPA1 activation in small cell lung cancer cells prevented apoptosis induced by serum starvation and thus promoted cell survival, an effect which could be blocked by inhibition of TRPA1 or ERK1/2 [165].

TRPP2, the ion channel mutated in autosomal dominant polycystic kidney disease, has been shown to protect cells from apoptosis by lowering the Ca^{2+} concentration in the ER [166]. ER-resident TRPP2 increases the ER permeability to Ca^{2+} and as such reduces Ca^{2+} release from the ER in response to apoptotic stimuli. Knockdown of TRPP2 in renal epithelial cells increases ER Ca^{2+} release and augments sensitivity to apoptosis [166].

Recently, the role of TRPML1 channels in Fas-mediated apoptosis in coronary arterial myocytes has been demonstrated [167]. Activation of Fas receptor by Fas ligand induced lysosomal Ca^{2+} release (through lysosomal TRPML1) followed by calcium release from sarcoplasmic reticulum and activation of calpains and calcineurin. Silencing of TRPML1 significantly attenuated FasL-induced apoptosis and activation of calpain and calcineurin, whereas TRPML1 overexpression enhanced them [167].

TRPML3 channel mutated in varitint-waddler mouse has been associated with apoptotic death of sensory hair cells [168]. The varitint-waddler mutation A419P renders TRPML3 constitutively active, resulting in sustained influx of Ca^{2+} and subsequent apoptosis. The cell death as well as intracellular level of Ca^{2+} was significantly reduced by expression of plasma membrane calcium ATPase PMCA2 [168]. Similar mechanism has been proposed also for TRPML2 [169].

Accumulated evidence strongly suggests the involvement TRP channels in the regulation of apoptosis. However, in many cases the precise mechanisms of such regulation are elusive, suggesting the need in future research in this area.

Voltage-gated calcium channels. Voltage-gated calcium channels (VGCC) mediate Ca^{2+} entry into cells in response to membrane depolarization [170]. Based on their activation threshold, they can be divided into two subgroups: low-voltage-activated (including L-, P/Q-, N- and R-types) and high-voltage-activated (T-type) channels [171]. VGCC are implicated in the regulation of various important physiological processes including gene transcription, muscle contraction, hormone secretion, and neurotransmitter release [170]. Several reports have connected VGCC to apoptosis regulation. Depolarization-triggered calcium entry through L-type calcium channels has been found to cause mitochondrial disruption and apoptosis in chromaffin cells [172]. Thus, it appears that L-type channels translate membrane depolarization into an apoptotic stimulus. Further, Bcl2 has been reported to increase apoptotic resistance of PC12 cells by reducing Ca^{2+} entry and mitochondrial Ca^{2+} overload through indirect downregulation of L-type Ca^{2+} channels [173]. L-type calcium channels have been also implicated in apoptosis of pancreatic beta cells in patients with insulin-dependent diabetes mellitus (IDDM) [174]. Serum from patients with IDDM increased L-type calcium channel activity and caused cytoplasmic Ca^{2+} overload, thus triggering apoptosis [174]. Similarly, low-voltage-activated (presumably T-type) calcium channel mediated cytokine-induced pancreatic beta-cell apoptosis through the increase in basal cytoplasmic free Ca^{2+} concentration [175]. In contrast, T-type Ca^{2+} channel inhibition has been reported to induce p53-dependent apoptosis through activation of p38-MAPK in colon cancer cells [176]. In malignant melanoma cells knockdown or pharmacological inhibition of T-type channels induced ER-stress, inhibited autophagy and stimulated caspase-dependent apoptosis [177]. In glioblastoma cells, inhibition of T-type calcium channels disrupted Akt signaling and promoted apoptosis via reduction in BAD phosphorylation and caspases activation [178]. However, in spermatogenic cells inhibition of T-type channels prevented 2,5-hexanedione-induced mitochondrial potential loss, reduced caspase-3 activity, and increased cell survival via increase in anti-apoptotic BCL-XL expression and decrease in proapoptotic BCL-XS expression [179].

Given the important role of T-type channels in the regulation of apoptosis as well as other cancer-related processes, these channels were proposed as attractive molecular targets for anticancer therapy [180]. However, considering differential role of VGCC in apoptosis regulation in different cell models, further studies are necessary to uncover specific mechanisms of such regulation in each particular case.

3.2. Potassium and potassium channels

One of the characteristic morphological features of apoptosis is cell shrinkage [1]. A number of studies have linked cell shrinkage to potassium ions loss. Indeed, being the predominant ion inside the cell K^+ ions

have been proposed to be major determinants of cell volume [181,182]. Moreover, cytoplasmic K^+ loss has been shown to favor activation of caspases and nucleases, which lead to apoptosis [183,184]. Indeed, several studies demonstrated that cellular K^+ depletion by valinomycin (K^+ ionophore) or plasma membrane K^+ channel overexpression induces apoptosis in different cell types [185–187]. Further, high extracellular K^+ has been reported to inhibit both the extrinsic and the intrinsic apoptosis, presumably by inhibiting the Cyt C release [188].

Potassium channels represent transmembrane proteins mediating the flow of potassium ions down their electrochemical gradient. K^+ channels are widely distributed in a vast variety of cells (both excitable and non-excitable) and are involved in a plethora of physiological processes including maintenance of membrane potential, cell proliferation and apoptosis [189,190]. Based on structural criteria, conductance properties as well as activation mechanisms potassium channels are divided into four classes: voltage-gated, calcium-activated, inward-rectifier and two-pore-domain potassium channels [189]. Various members of these four classes have been implicated in apoptosis regulation. For the complete list of potassium channels involved in the regulation of apoptosis we refer the reader to the comprehensive reviews on this subject [190–194]. Here we provide a brief overview of this area of research.

Given that K^+ efflux has been proposed to be a pro-apoptotic factor, plasma membrane potassium channels mediating K^+ efflux out of the cell represent good candidates for apoptosis regulation. However, considering uneven distribution of K^+ channels among different cell types, the specific channel that is involved varies, depending on apoptotic stimulus and cell type. For example, Kv2.1 channels have been shown to be responsible for oxidant and staurosporine-induced apoptosis in neurons [195]. In contrast, in glioblastoma cells intermediate-conductance calcium-activated potassium (IK) channel is implicated in the staurosporine-activated intrinsic apoptotic pathway while large-conductance calcium-activated potassium (BK) channels were reported to be responsible for extrinsic apoptosis [196]. In neurons, syntaxin-dependent incorporation of Kv2.1 voltage-gated potassium channels into the plasma membrane has been shown to mediate K^+ current increase during apoptosis. Both p38 MAPK and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) have been implicated in this process [197,198].

In vascular smooth muscle cells, disruption of mitochondrial homeostasis by carbonyl cyanide-p-trifluoromethoxyphenyl-hydrazone (FCCP) induced apoptosis which was connected to an increase in BK channel activity [185]. Moreover, activation of BKCa channels has been implicated in TNFα- and nitric oxide-induced apoptosis [199,200]. HERG conductance has been demonstrated to promote hydrogen peroxide-induced apoptosis of various tumor cells [201].

Members of two-pore-domain potassium channels have been also reported to contribute to apoptotic cell death [202]. For example, TWIK-related acid-sensitive potassium channel 3 (TASK3) has been shown to contribute to TNFα-induced apoptosis in a JNK- and p38-dependent way [203]. Both TASK1 and TASK3 have been also implicated in K^+-dependent apoptosis of cerebellar granule neurons [204]. Furthermore, hydrogen peroxide-mediated apoptosis was associated with activation of TREK channels [205].

Activation of K^+ channels by Cyt C has been proposed to play an important role in initiating the apoptotic volume decrease when cells undergo apoptosis [206]. Overexpression of BCL-2 accelerated the inactivation and downregulated the mRNA of Kv1.1, Kv1.5, and Kv2.1 channels in vascular smooth muscle cells, thus representing an additional mechanism involved in the BCL-2-mediated anti-apoptotic effect [207].

A set of K^+ channels has been found to be localized on mitochondrial membranes [208]. These channels include inward rectifying channel (Kir), ATP-dependent potassium channel (KATP), BKCa, IKCa, Kv1.3 and TASK3 [209]. Mitochondrial potassium channels regulate mitochondrial volume, mitochondrial ROS production and ATP synthesis [209]. Thus, alterations in these channels could lead to the disturbance in mitochondrial homeostasis and subsequently to apoptosis. Indeed, mitochondrial potassium channels have been implicated in apoptosis regulation in variety of cell types. For example, mitochondrial potassium channel Kv1.3 has been suggested to mediate BAX-induced apoptosis in lymphocytes [210]. BAX has been shown to interact with and inhibit mitochondrial Kv1.3, that triggered hyperpolarization, formation of reactive oxygen species, release of Cyt C and apoptosis [210]. Similar mechanism was proposed to be shared by other mitochondrial Kvs, namely Kv1.1 and Kv1.5 [211]. Moreover, pharmacological inhibitors of mitochondrial Kv1.3 were recently reported to induce cancer cell apoptosis independently of BAX and BAK expression. More specifically, Psora-4, PAP-1 or clofazimine (membrane-permeant Kv1.3 inhibitors) efficiently induced apoptosis in Bax/Bak-double deficient human Jurkat leukemic T cells as well as in Bax/Bak-double knock-out murine embryonic fibroblasts [212,213].

Recently, despite the widely appreciated role of K^+ efflux in apoptosis, it was proposed that intracellular K^+ concentration decrease is not obligatory for apoptosis [214]. The authors showed that in Xenopus oocytes caspase-3 activity is not dependent on the intracellular concentration of K^+ and suggested that there is no causal link between the K^+ reduction and the caspase-dependent apoptotic process [214].

Considering their role in apoptosis regulation, potassium channels have gained much of attention as potential regulators of cancer cell death and promising anticancer therapeutic targets. Aberrant expression of potassium channels is frequently observed in different cancers [192]. However, some cancers are characterized by increased expression of some potassium channels, while others show down-regulation, suggesting cell-type-specific functions of these channels [215–217]. Thus, it seems that the contribution of potassium channels to the regulation of apoptosis in cancer could vary depending on cancer type, potassium channel type, expression levels, intracellular localization as well as regulation by pro- or anti-apoptotic factors.

3.3. Sodium and sodium channels

Along with K^+ ions which have been proposed to be critical determinants of cell volume and apoptosis, other monovalent ions, including Na^+ and Cl^-, have been also demonstrated to play the role in apoptosis. Accumulated data suggest that an increase in intracellular Na^+ occurs early in apoptosis [218,219]. Moreover, several studies also reported a late increase in cytoplasmic Na^+ in apoptotic cells [220,221]. Interestingly, in the absence of physiological levels of extracellular sodium apoptotic stimulation resulted in Jurkat T-cell swelling and not cell shrinkage, suggesting that sodium controls cell morphology during apoptosis [222]. However, despite swelling these cells showed all the other characteristic features of apoptosis, such as caspase activity, DNA fragmentation and phosphatidylserine externalization [222].

Sodium influx has been suggested to contribute to plasma membrane depolarization frequently observed early in apoptosis [223,224]. However, sodium was not involved in anti-Fas induced depolarization, while mediating depolarization early in of arsenic trioxide-induced apoptosis in myeloid cells. Thus, the existence of different mechanisms for apoptotic plasma membrane depolarization within one cell type has been suggested [224].

Sodium has been also implicated in early phosphatidylserine exposure triggered by purinoreceptor P2X7 activation in thymocytes [225]. Moreover, it has been proposed that intracellular sodium may control K^+ efflux during apoptosis via stimulation of muscarinic K^+ channel (KACh) [226] as well as G protein-gated K^+ channels (GIRK, or Kir3) [227].

Sodium channels represent the integral membrane proteins mediating the influx of Na^+ ions into the cell. According to the mechanism of activation sodium channels could be classified into voltage-gated

sodium channels (VGSC) and voltage-independent sodium channels comprising epithelial sodium channels (ENaCs), acid-sensing sodium channels (ASICs) and sodium leak channel NALCN [228–231]. However, despite understanding of the important role Na^+ ions play in apoptosis, the data on the involvement of sodium channels in apoptosis regulation are rather scarce.

Activation of voltage-sensitive sodium channels during oxygen deprivation has been demonstrated to lead to apoptotic caspase-3-dependent neuronal death, whereas inhibition of sodium channels by tetrodotoxin (TTX) attenuated caspase-3 activation and apoptosis [232]. The sodium channel modulator veratridine has been shown to induce neuronal apoptosis, which could be prevented by TTX. The reported mechanism involves Ca^{2+}, mitochondria, reactive oxygen species and p53 activation [233]. In line with this, AM-36, a neuroprotective agent incorporating both antioxidant and sodium channel blocking actions, completely inhibited veratridine-induced neuronal toxicity [234]. Saxitoxin, a sodium channel blocker, has been shown to prevent anti-Fas induced apoptosis in Jurkat T-cells by preventing sodium influx [222].

Interestingly, the expression/function of the shrinkage-activated ENaC has been reported in rat hepatocytes [235]. During cell shrinkage this channel is activated by the cell volume-sensitive serine/threonine kinase hSGK. This mechanism could contribute to the increase in intracellular sodium during apoptosis [235].

Blockade of ASICs by amiloride has been suggested to protect articular chondrocytes from acid-induced apoptotic injury [236,237]. However, in these studies pro-apoptotic role of ASICs has been explained by calcium-permeability of these channels. Thus, acidosis triggers ASIC-mediated calcium influx which induces apoptosis by mitochondria- or calpain/calcineurin-dependent pathways. Inhibition of this calcium influx by amiloride prevented acid-induced apoptosis [236,237]. Calcium-permeable ASIC1a has been also implicated in acid-induced neuronal cell death [238,239].

Functional expression of sodium channels has been reported in different cancers, including those of prostate, breast, colon, lung, skin and others [240]. Aberrant expression of some sodium channels has been also demonstrated in several cancers [241,242]. However, pharmacological targeting of sodium channels in cancer commonly results in the changes in metastatic behavior of cancer cells without significant effects on viability. It should be noted that nonselective cation channels, for example the members of TRP channels family, are also permeable for Na^+ ions, suggesting that these channels could potentially regulate apoptosis by Na^+-dependent mechanisms.

3.4. Chloride and chloride channels

As it was previously mentioned, cell shrinkage or apoptotic volume decrease (AVD) represents one of the characteristic morphological features of apoptosis. Chloride ions are inextricably linked to this phenomenon. Numerous studies have demonstrated that during AVD chloride ions leave the cell similarly to potassium ions [181,243,244]. A variety of apoptotic stimuli in different cell types have been shown to induce activation of chloride currents. Importantly, inhibition of these currents was found to prevent AVD and inhibit apoptotic cell death [243,245,246].

Chloride flow across the cell membranes is mediated by chloride channels. The Cl^- channels are ubiquitously expressed and participate in many physiological processes including volume regulation, acidification of intracellular organelles, cell cycle and apoptosis [247]. According to the gating mechanisms chloride channels could be classified into voltage-gated chloride channels (the ClC family), cystic fibrosis transmembrane conductance regulator (CFTR), Ca^{2+}-activated chloride channels (CaCCs), volume-regulated anion channels (VRACs) and ligand gated anion channels [247]. It should be noted that chloride channels are permeable for various anions, suggesting that other ions along with Cl^- could mediate the final effects of channels opening. However, given that Cl^- is the most abundant anion in all organisms it is widely accepted that Cl^- constitutes the predominant ion passing through chloride channels [248].

The most studied Cl^- channels for their role in AVD and apoptosis are volume-regulated anion channels (VRACs). VRACs have been implicated in regulatory volume decrease (RVD) in response to hypoosmotic stress-induced cell swelling [249]. Cell swelling activates VRACs, which mediate Cl^- efflux (accompanied by K^+ efflux through potassium channels) resulting in osmotic-driven H_20 efflux and cell volume restoration. Given that AVD is accompanied by Cl^- ions loss, it is not surprising that VRACs have been implicated in apoptotic pathway. Thus, VRACs activation (alternatively named volume-sensitive outwardly rectifying (VSOR) chloride channels) have been observed in a wide variety of cell types in response to a number of apoptotic stimuli [245]. For example, it has been demonstrated that both mitochondria- and death receptor-mediated apoptosis inducers (staurosporine and Fas ligand or TNFα) activate chloride currents in human epithelial HeLa cells [250]. These currents exhibited the properties characteristic of VSOR currents, including outward rectification, inhibition by cell shrinkage, sensitivity to chloride channel blockers, and dependence on cytosolic ATP [250]. Thus, it appears that during AVD VSORs are highly sensitized and could be activated even in non-swollen cells. Several mechanisms have been proposed to explain this increased sensitivity of VSORs, including modulation by ROS [250] and cytosolic ATP [251].

Importantly, pharmacological inhibition of VSORs by DIDS, SITS, NPPB or phloretin prevented staurosporine-, TNFα-, or Fas ligand-induced AVD in various cell types [243,252]. Inhibition of apoptotic cell death by VSOR blockers has been also reported [245]. However several reports demonstrated that VSOR blockers could prevent AVD without inhibiting apoptotic cell death. For example, induction of apoptosis by nitric oxide in macrophages was reported to be independent of AVD and was not prevented by VSOR channel blockers phloretin and SITS [253]. In line with this, staurosporine-, C2-ceramide-, or serum deprivation-induced AVD was completely prevented by DIDS, SITS, or NPPB Cl^- channel blockers in cortical neurons, whereas apoptotic cell death induced by these stimuli was only mildly attenuated [244]. The authors attributed observed effects to ClC-2 and ClC-3 chloride channels, found to be expressed in cortical neurons. On the other hand, K^+ channel blockers tetraethylammonium (TEA) or clofilium completely prevented both AVD and apoptotic cell death [244].

Moreover, inhibitory effect of Cl^- channel blockers on both AVD and apoptosis was also demonstrated in cancer. In human epidermoid cancer cells, Cl^- channel blockers SITS and DIDS reduced cisplatin-induced apoptotic death [254]. Conversely, VSOR activity restoration resulted in increased apoptotic cell death following cisplatin treatment [255]. Accordingly, dysfunction of VRACs has been reported to contribute to cisplatin resistance in human lung adenocarcinoma cells [256].

Despite the fact, that VRACs have been found to be ubiquitously expressed and are implicated in various physiological processes, the molecular identity of VRACs is not clear. The ClC-3 protein has been proposed as one of the molecular candidates for the role of VRAC [257]. In HeLa cells and Xenopus laevis oocytes knockdown of ClC-3 significantly reduced the density of cell swelling-induced VRAC current as well as impaired the ability of cells to regulate their volume [258]. In prostate cancer LNCaP cells ClC-3-specific antibody suppressed swelling-activated Cl^- current [259]. Unexpectedly, overexpression of BCL-2 in these cells resulted in an increase in swelling-activated Cl^- current and an enhancement of endogenous expression of ClC-3 protein. The authors suggested that increase in ClC-3 expression would strengthen the ability of the cells to handle proliferative volume increases and thereby promote their survival and diminish their proapoptotic potential [259]. This hypothesis was further strengthened by the finding, that apoptosis-resistant neuroendocrine (NE) differentiated LNCaP cells were characterized by the enhanced expression of ClC-3 as well as augmented swelling-activated Cl^- current [260]. Consistent with this, overexpression of ClC-3 inhibited TGF-beta1-induced in human

bronchial epithelial cells apoptosis [261]. In neuroendocrine tumor cell lines (BON, LCC-18, and QGP-1) ClC-3 expression has been reported to enhance etoposide resistance by increasing acidification of the late endocytic compartment [262]. Indeed, as it was shown earlier, ClC-3 represents intracellular chloride channel, mainly residing on endosomal compartments [263].

However, no significant difference in swelling-activated currents (recorded in mouse hepatocytes and pancreatic acinar cells) has been observed between wild-type and ClC-3-KO mice, indicating that ClC-3 does not underlie VRAC [263]. Consistent with this, several other studies confirmed that functional expression of VRAC in the plasma membrane is independent of the molecular expression of ClC-3 in different cell types [264,265].

Several other chloride channels have been also implicated in apoptosis regulation. Anoctamin 6 (ANO6, or TMEM16F), a calcium-activated anion channel, has been reported to be an essential component of the outwardly rectifying chloride channel activated during apoptosis [266]. However, it has been shown that ANO6 activity is not related to VSOR [267]. Nevertheless, in a recent study it has been demonstrated that ANO6 differs from VRAC but supports volume regulation in the presence of Ca^{2+} [268]. Moreover, ANO6 is involved in cisplatin-induced apoptosis in Ehrlich–Lettre ascites (ELA) cells, as knockdown of ANO6 in ELA cells resulted in a decrease in cisplatin-induced caspase-3 activity, suggesting proapoptotic role for ANO6 [268]. Further, ANO6 has been suggested as an essential component for the Ca^{2+}-dependent exposure of phosphatidylserine on the cell surface, indicating another mechanism for ANO6 to regulate apoptosis [269].

Cystic fibrosis transmembrane conductance regulator (CFTR), loss of function mutations of which cause the autosomal recessive lethal disease cystic fibrosis, represents a cAMP-dependent chloride channel. Along with chloride channel function CFTR has been shown to modulate other ion channels and transporters [248]. CFTR was reported to contribute to cisplatin-induced apoptosis renal proximal cells, as blockade of CFTR by the specific inhibitor CFTRinh-172 prevented cisplatin-induced increase of ROS, decrease of intracellular GSH content and activation of caspase-3 [270]. In Chinese hamster lung fibroblasts CFTR has been demonstrated to enhance apoptosis, probably due to the modulation of the Cl^-/HCO^-_3 exchanger, resulting in a more efficient intracellular acidification [271]. Interestingly CFTR augmented chloride current produced by pro-apoptotic Ano6 in airway epithelial cells, suggesting its pro-apoptotic function [266].

mtCLIC/CLIC4 is an intracellular chloride channel associated with the inner mitochondrial membrane, ER membrane, nucleus and cytoplasm. CLIC4 is regulated by p53 and TNFα [272]. DNA damage or overexpression of p53 have been reported to upregulate CLIC4 and induce apoptosis. Overexpression of CLIC4 was demonstrated to induce apoptosis via caspase-dependent mitochondrial apoptotic pathway. Conversely, decrease in CLIC4 expression reduced p53-induced apoptosis [272]. Further, multiple stress inducers were found to cause the translocation of cytoplasmic CLIC4 to the nucleus, thereby accelerating apoptosis [273]. In line with this, CLIC4 expression is reduced in mouse and human skin cancer cell lines and the protein is excluded from the nucleus, thus contributing to TGF-β resistance and enhancing tumor development [274].

4. Conclusions

It has long been known that apoptosis plays a crucial role in physiology. Thus, apoptotic machinery has been studied in great detail and includes a variety of molecular players. Cytoplasmic and extracellular ion concentrations as well as ion channels, mediating ion fluxes across cellular membranes, have emerged as important regulators of apoptosis (Fig. 1).

Accumulated data proves that both ion channels and apoptosis dysfunctions are implicated in cancer initiation and progression as well as chemotherapy resistance. This fact explains the constantly growing interest in understanding the interplay between ion channels and apoptosis in cancer.

Current evidence suggests the altered expression of various ion channels in cancer. This has been linked to a number of cancer-related processes, including apoptosis. Thus, ion channels have been proposed as promising therapeutic targets for repairing defective apoptosis in cancer. However, despite the essential progress achieved in this field, the practical utility of targeting ion channels for cancer treatment remains very limited.

One of the reasons is that most ion channels have broad expression patterns and thus are not cancer-specific. Therefore, selective targeting is vitally important to prevent toxicity to normal cells, induced by the pharmacological impairment of channel function. Another issue is unavailability of highly selective pharmacological modulators for most ion channels. The existence of alternatively spliced variants of many channels further complicates the situation. Thus, novel selective pharmacological agents, drug delivery techniques as well as siRNA transfection technologies are clearly needed to finally see the clinical implications of ion channels targeting in cancer therapy.

Further, most ion channels that have a role in apoptosis have been also implicated in other cancer-related processes, such as proliferation, differentiation and migration. This fact should be considered when targeting apoptosis through ion channels in cancer treatment.

One of the major obstacles preventing the announcement of ion channel targeting as a general approach to treat cancer is differential and paradoxical contribution of specific ion channels to apoptosis depending on cancer type, ion channel type, expression levels and intracellular localization, as well as regulation by pro- or anti-apoptotic factors.

Indeed, given that Cl^- ions loss is an important pro-apoptotic factor, one could expect the downregulation or inhibition of VRACs in cancer cells to prevent apoptosis. However, ClC-3 has been found to be overexpressed in apoptosis-resistant prostate cancer cells and to enhance etoposide-resistance in neuroendocrine tumor cell lines. On the other hand, VRACs positively contribute to cisplatin-induced apoptosis in epidermoid cancer cells as well as human lung adenocarcinoma cells.

Further, while it's generally accepted that cytosolic and mitochondrial Ca^{2+} overload represents a strong apoptotic stimulus, it is logical to assume that cancer cells will downregulate Ca^{2+}-permeable channels to reduce Ca^{2+} influx. While this is the case for some channels such as TRPM2 and TRPV1, a number of Ca^{2+}-permeable channels have been demonstrated to be overexpressed in cancer, including TRPM8, TRPV2 and TRPV6.

Similarly, the downregulation of K^+ channels by cancer cells would be expected, as K^+ efflux promotes apoptosis. However, this is not the case for all the cancers, as elevated expression of $K_v11.1$, $K_{2P}1.1$, $K_{2P}3.1$ and other channels has been reported in several cancers.

Moreover, one given channel could play opposite roles in apoptosis in different cancer types. For example, TRPM8 activation by menthol was reported to decrease the viability of melanoma cells as well as human bladder cancer cells. In contrast, TRPM8 silencing enhanced epirubicin-induced apoptosis in human osteosarcoma cells. Further, TRPC1 overexpression has been found to sensitize intestinal epithelial cells to apoptosis, while protecting human neuroblastoma cells against salsolinol-induced apoptosis. The two isoforms of IP_3R have been also demonstrated to oppositely regulate apoptosis. Thus, the anti-apoptotic role for IP_3R type III has been proposed in colorectal carcinoma, contrasting with the pro-apoptotic role of IP_3R type I in bladder cancer cells.

Taken together, the data presented here clearly demonstrate the diversity and particular importance of ion channels in apoptosis regulation. These channels belong to different families, control the flow of different classes of ions across cell membranes, have different gating mechanisms as well as biophysical properties, and show different localization patterns. Ion channels have been implicated in virtually all decisive aspects of apoptotic process, such as cell shrinkage, cytoplasmic, ER

and mitochondrial calcium signaling, as well as mitochondrial depolarization and integrity. Importantly, the contribution of specific ion channels to apoptosis in cancer could vary depending on multiple factors such as cancer type and stage, ion channel type and localization, as well as intracellular signaling pathways involved. Therefore, no general approach can be proposed to fight cancer by ion channel targeting. Each particular cancer case requires a personal approach. Thus, we conclude that ion channels targeting has good prospects as a potential specific tool for personalized cancer therapy.

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References

[1] J.F. Kerr, A.H. Wyllie, A.R. Currie, Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics, Br. J. Cancer 26 (1972) 239–257.
[2] M. Suzanne, H. Steller, Shaping organisms with apoptosis, Cell Death Differ. 20 (2013) 669–675.
[3] J. Yuan, B.A. Yankner, Apoptosis in the nervous system, Nature 407 (2000) 802–809.
[4] R. Hernandez-Martinez, L. Covarrubias, Interdigital cell death function and regulation: new insights on an old programmed cell death model, Dev. Growth Differ. 53 (2011) 245–258.
[5] P. Bouillet, J.F. Purton, D.I. Godfrey, L.C. Zhang, L. Coultas, H. Puthalakath, M. Pellegrini, S. Cory, J.M. Adams, A. Strasser, BH3-only Bcl-2 family member Bim is required for apoptosis of autoreactive thymocytes, Nature 415 (2002) 922–926.
[6] M. Pellegrini, G. Belz, P. Bouillet, A. Strasser, Shutdown of an acute T cell immune response to viral infection is mediated by the proapoptotic Bcl-2 homology 3-only protein Bim, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 14175–14180.
[7] C.B. Thompson, Apoptosis in the pathogenesis and treatment of disease, Science 267 (1995) 1456–1462.
[8] T.G. Cotter, Apoptosis and cancer: the genesis of a research field, Nat. Rev. Cancer 9 (2009) 501–507.
[9] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[10] C. Dubois, F. Vanden Abeele, N. Prevarskaya, Targeting apoptosis by the remodelling of calcium-transporting proteins in cancerogenesis, FEBS J. 280 (2013) 5500–5510.
[11] S. Fulda, Targeting apoptosis for anticancer therapy, Semin. Cancer Biol. (2014).
[12] F. Lang, M. Foller, K.S. Lang, P.A. Lang, M. Ritter, E. Gulbins, A. Vereninov, S.M. Huber, Ion channels in cell proliferation and apoptotic cell death, J. Membr. Biol. 205 (2005) 147–157.
[13] M.A. Razik, J.A. Cidlowski, Molecular interplay between ion channels and the regulation of apoptosis, Biol. Res. 35 (2002) 203–207.
[14] F. Lang, A. Lepple-Wienhues, M. Paulmichl, I. Szabo, D. Siemen, E. Gulbins, Ion channels, cell volume, and apoptotic cell death, Cell. Physiol. Biochem. 8 (1998) 285–292.
[15] L. Leanza, L. Biasutto, A. Manago, E. Gulbins, M. Zoratti, I. Szabo, Intracellular ion channels and cancer, Front. Physiol. 4 (2013) 227.
[16] N. Prevarskaya, R. Skryma, Y. Shuba, Ion channels and the hallmarks of cancer, Trends Mol. Med. 16 (2010) 107–121.
[17] S. Elmore, Apoptosis: a review of programmed cell death, Toxicol. Pathol. 35 (2007) 495–516.
[18] R.C. Taylor, S.P. Cullen, S.J. Martin, Apoptosis: controlled demolition at the cellular level, Nat. Rev. Mol. Cell Biol. 9 (2008) 231–241.
[19] M.O. Hengartner, The biochemistry of apoptosis, Nature 407 (2000) 770–776.
[20] L. Galluzzi, I. Vitale, J.M. Abrams, E.S. Alnemri, E.H. Baehrecke, M.V. Blagosklonny, T.M. Dawson, V.L. Dawson, W.S. El-Deiry, S. Fulda, E. Gottlieb, D.R. Green, M.O. Hengartner, O. Kepp, R.A. Knight, S. Kumar, S.A. Lipton, X. Lu, F. Madeo, W. Malorni, P. Mehlen, G. Nunez, M.E. Peter, M. Piacentini, D.C. Rubinsztein, Y. Shi, H.U. Simon, P. Vandenabeele, E. White, J. Yuan, B. Zhivotovsky, G. Melino, G. Kroemer, Molecular definitions of cell death subroutines: recommendations of the Nomenclature Committee on Cell Death 2012, Cell Death Differ. 19 (2012) 107–120.
[21] S.W. Tait, D.R. Green, Mitochondria and cell death: outer membrane permeabilization and beyond, Nat. Rev. Mol. Cell Biol. 11 (2010) 621–632.
[22] C. Brenner, S. Grimm, The permeability transition pore complex in cancer cell death, Oncogene 25 (2006) 4744–4756.
[23] I. Szabo, M. Zoratti, Mitochondrial channels: ion fluxes and more, Physiol. Rev. 94 (2014) 519–608.
[24] G. Kroemer, L. Galluzzi, C. Brenner, Mitochondrial membrane permeabilization in cell death, Physiol. Rev. 87 (2007) 99–163.
[25] P. Li, D. Nijhawan, I. Budihardjo, S.M. Srinivasula, M. Ahmad, E.S. Alnemri, X. Wang, Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade, Cell 91 (1997) 479–489.
[26] J. Chai, C. Du, J.W. Wu, S. Kyin, X. Wang, Y. Shi, Structural and biochemical basis of apoptotic activation by Smac/DIABLO, Nature 406 (2000) 855–862.
[27] S.M. Srinivasula, S. Gupta, P. Datta, Z. Zhang, R. Hegde, N. Cheong, T. Fernandes-Alnemri, E.S. Alnemri, Inhibitor of apoptosis proteins are substrates for the mitochondrial serine protease Omi/HtrA2, J. Biol. Chem. 278 (2003) 31469–31472.
[28] R. Hegde, S.M. Srinivasula, Z. Zhang, R. Wassell, R. Mukattash, L. Cilenti, G. DuBois, Y. Lazebnik, A.S. Zervos, T. Fernandes-Alnemri, E.S. Alnemri, Identification of Omi/HtrA2 as a mitochondrial apoptotic serine protease that disrupts inhibitor of apoptosis protein–caspase interaction, J. Biol. Chem. 277 (2002) 432–438.
[29] N. Joza, S.A. Susin, E. Daugas, W.L. Stanford, S.K. Cho, C.Y. Li, T. Sasaki, A.J. Elia, H.Y. Cheng, L. Ravagnan, K.F. Ferri, N. Zamzami, A. Wakeham, R. Hakem, H. Yoshida, Y.Y. Kong, T.W. Mak, J.C. Zuniga-Pflucker, G. Kroemer, J.M. Penninger, Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death, Nature 410 (2001) 549–554.
[30] L.Y. Li, X. Luo, X. Wang, Endonuclease G is an apoptotic DNase when released from mitochondria, Nature 412 (2001) 95–99.
[31] H. Wajant, The Fas signaling pathway: more than a paradigm, Science 296 (2002) 1635–1636.
[32] H. Walczak, M.R. Sprick, Biochemistry and function of the DISC, Trends Biochem. Sci. 26 (2001) 452–453.
[33] H. Li, H. Zhu, C.J. Xu, J. Yuan, Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis, Cell 94 (1998) 491–501.
[34] X. Luo, I. Budihardjo, H. Zou, C. Slaughter, X. Wang, Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors, Cell 94 (1998) 481–490.
[35] P. Mehlen, D.E. Bredesen, Dependence receptors: from basic research to drug development, Sci. Signal. 4 (2011) mr2.
[36] M.J. Berridge, P. Lipp, M.D. Bootman, The versatility and universality of calcium signalling, Nat. Rev. Mol. Cell Biol. 1 (2000) 11–21.
[37] S. Orrenius, B. Zhivotovsky, P. Nicotera, Regulation of cell death: the calcium-apoptosis link, Nat. Rev. Mol. Cell Biol. 4 (2003) 552–565.
[38] P. Pinton, C. Giorgi, R. Siviero, E. Zecchini, R. Rizzuto, Calcium and apoptosis: ER-mitochondria Ca2+ transfer in the control of apoptosis, Oncogene 27 (2008) 6407–6418.
[39] C. Giorgi, F. Baldassari, A. Bononi, M. Bonora, E. De Marchi, S. Marchi, S. Missiroli, S. Patergnani, A. Rimessi, J.M. Suski, M.R. Wieckowski, P. Pinton, Mitochondrial Ca(2+) and apoptosis, Cell Calcium 52 (2012) 36–43.
[40] G. Hajnoczky, G. Csordas, S. Das, C. Garcia-Perez, M. Saotome, S. Sinha Roy, M. Yi, Mitochondrial calcium signalling and cell death: approaches for assessing the role of mitochondrial Ca2+ uptake in apoptosis, Cell Calcium 40 (2006) 553–560.
[41] M. Chen, H. He, S. Zhan, S. Krajewski, J.C. Reed, R.A. Gottlieb, Bid is cleaved by calpain to an active fragment in vitro and during myocardial ischemia/reperfusion, J. Biol. Chem. 276 (2001) 30724–30728.
[42] S. Gil-Parrado, A. Fernandez-Montalvan, I. Assfalg-Machleidt, O. Popp, F. Bestvater, A. Holloschi, T.A. Knoch, E.A. Auerswald, K. Welsh, J.C. Reed, H. Fritz, P. Fuentes-Prior, E. Spiess, G.S. Salvesen, W. Machleidt, Ionomycin-activated calpain triggers apoptosis. A probable role for Bcl-2 family members, J. Biol. Chem. 277 (2002) 27217–27226.
[43] H.G. Wang, N. Pathan, I.M. Ethell, S. Krajewski, Y. Yamaguchi, F. Shibasaki, F. McKeon, T. Bobo, T.F. Franke, J.C. Reed, Ca2+-induced apoptosis through calcineurin dephosphorylation of BAD, Science 284 (1999) 339–343.
[44] N. Morishima, K. Nakanishi, H. Takenouchi, T. Shibata, Y. Yasuhiko, An endoplasmic reticulum stress-specific caspase cascade in apoptosis. Cytochrome c-independent activation of caspase-9 by caspase-12, J. Biol. Chem. 277 (2002) 34287–34294.
[45] T. Nakagawa, H. Zhu, N. Morishima, E. Li, J. Xu, B.A. Yankner, J. Yuan, Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta, Nature 403 (2000) 98–103.
[46] T. Nakagawa, J. Yuan, Cross-talk between two cysteine protease families. Activation of caspase-12 by calpain in apoptosis, J. Cell Biol. 150 (2000) 887–894.
[47] J.D. Robertson, S. Orrenius, B. Zhivotovsky, Review: nuclear events in apoptosis, J. Struct. Biol. 129 (2000) 346–358.
[48] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nat. Rev. Mol. Cell Biol. 4 (2003) 517–529.
[49] R. Rizzuto, D. De Stefani, A. Raffaello, C. Mammucari, Mitochondria as sensors and regulators of calcium signalling, Nat. Rev. Mol. Cell Biol. 13 (2012) 566–578.
[50] P. Bernardi, S. von Stockum, The permeability transition pore as a Ca(2+) release channel: new answers to an old question, Cell Calcium 52 (2012) 22–27.
[51] S.F. Pedersen, G. Owsianik, B. Nilius, TRP channels: an overview, Cell Calcium 38 (2005) 233–252.
[52] J.K. Foskett, C. White, K.H. Cheung, D.O. Mak, Inositol trisphosphate receptor Ca2+ release channels, Physiol. Rev. 87 (2007) 593–658.
[53] S.K. Joseph, G. Hajnoczky, IP3 receptors in cell survival and apoptosis: Ca2+ release and beyond, Apoptosis 12 (2007) 951–968.
[54] S. Blackshaw, A. Sawa, A.H. Sharp, C.A. Ross, S.H. Snyder, A.A. Khan, Type 3 inositol 1,4,5-trisphosphate receptor modulates cell death, FASEB J. 14 (2000) 1375–1379.
[55] T. Jayaraman, A.R. Marks, T cells deficient in inositol 1,4,5-trisphosphate receptor are resistant to apoptosis, Mol. Cell. Biol. 17 (1997) 3005–3012.
[56] A.A. Khan, M.J. Soloski, A.H. Sharp, G. Schilling, D.M. Sabatini, S.H. Li, C.A. Ross, S.H. Snyder, Lymphocyte apoptosis: mediation by increased type 3 inositol 1,4,5-trisphosphate receptor, Science 273 (1996) 503–507.

[57] R. Rizzuto, S. Marchi, M. Bonora, P. Aguiari, A. Bononi, D. De Stefani, C. Giorgi, S. Leo, A. Rimessi, R. Siviero, E. Zecchini, P. Pinton, Ca(2+) transfer from the ER to mitochondria: when, how and why, Biochim. Biophys. Acta 1787 (2009) 1342–1351.
[58] J.E. Vance, Phospholipid synthesis in a membrane fraction associated with mitochondria, J. Biol. Chem. 265 (1990) 7248–7256.
[59] C. Cardenas, R.A. Miller, I. Smith, T. Bui, J. Molgo, M. Muller, H. Vais, K.H. Cheung, J. Yang, I. Parker, C.B. Thompson, M.J. Birnbaum, K.R. Hallows, J.K. Foskett, Essential regulation of cell bioenergetics by constitutive InsP3 receptor Ca2+ transfer to mitochondria, Cell 142 (2010) 270–283.
[60] R. Rizzuto, M. Brini, M. Murgia, T. Pozzan, Microdomains with high Ca2+ close to IP3-sensitive channels that are sensed by neighboring mitochondria, Science 262 (1993) 744–747.
[61] R. Rizzuto, P. Pinton, W. Carrington, F.S. Fay, K.E. Fogarty, L.M. Lifshitz, R.A. Tuft, T. Pozzan, Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses, Science 280 (1998) 1763–1766.
[62] K.J. Alzayady, R. Chandrasekhar, D.I. Yule, Fragmented inositol 1,4,5-trisphosphate receptors retain tetrameric architecture and form functional Ca2+ release channels, J. Biol. Chem. 288 (2013) 11122–11134.
[63] J. Hirota, T. Furuichi, K. Mikoshiba, Inositol 1,4,5-trisphosphate receptor type 1 is a substrate for caspase-3 and is cleaved during apoptosis in a caspase-3-dependent manner, J. Biol. Chem. 274 (1999) 34433–34437.
[64] C.M. Kopil, H. Vais, K.H. Cheung, A.P. Siebert, D.O. Mak, J.K. Foskett, R.W. Neumar, Calpain-cleaved type 1 inositol 1,4,5-trisphosphate receptor (InsP(3)R1) has InsP(3)-independent gating and disrupts intracellular Ca(2+) homeostasis, J. Biol. Chem. 286 (2011) 35998–36010.
[65] K. Szlufcik, L. Missiaen, J.B. Parys, G. Callewaert, H. De Smedt, Uncoupled IP3 receptor can function as a Ca2+-leak channel: cell biological and pathological consequences, Biol. Cell 98 (2006) 1–14.
[66] D. Boehning, R.L. Patterson, L. Sedaghat, N.O. Glebova, T. Kurosaki, S.H. Snyder, Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis, Nat. Cell Biol. 5 (2003) 1051–1061.
[67] H. Akl, G. Bultynck, Altered Ca(2+) signaling in cancer cells: proto-oncogenes and tumor suppressors targeting IP3 receptors, Biochim. Biophys. Acta 1835 (2013) 180–193.
[68] S. Marchi, M. Marinello, A. Bononi, M. Bonora, C. Giorgi, A. Rimessi, P. Pinton, Selective modulation of subtype III IP(3)R by Akt regulates ER Ca(2)(+) release and apoptosis, Cell Death Dis. 3 (2012) e304.
[69] A. Bononi, M. Bonora, S. Marchi, S. Missiroli, F. Poletti, C. Giorgi, P.P. Pandolfi, P. Pinton, Identification of PTEN at the ER and MAMs and its regulation of Ca(2+) signaling and apoptosis in a protein phosphatase-dependent manner, Cell Death Differ. 20 (2013) 1631–1643.
[70] C. Giorgi, K. Ito, H.K. Lin, C. Santangelo, M.R. Wieckowski, M. Lebiedzinska, A. Bononi, M. Bonora, J. Duszynski, R. Bernardi, R. Rizzuto, C. Tacchetti, P. Pinton, P.P. Pandolfi, PML regulates apoptosis at endoplasmic reticulum by modulating calcium release, Science 330 (2010) 1247–1251.
[71] K. Shibao, M.J. Fiedler, J. Nagata, N. Minagawa, K. Hirata, Y. Nakayama, Y. Iwakiri, M.H. Nathanson, K. Yamaguchi, The type III inositol 1,4,5-trisphosphate receptor is associated with aggressiveness of colorectal carcinoma, Cell Calcium 48 (2010) 315–323.
[72] S.S. Kang, K.S. Han, B.M. Ku, Y.K. Lee, J. Hong, H.Y. Shin, A.G. Almonte, D.H. Woo, D.J. Brat, E.M. Hwang, S.H. Yoo, C.K. Chung, S.H. Park, S.H. Paek, E.J. Roh, S.J. Lee, J.Y. Park, S.F. Traynelis, C.J. Lee, Caffeine-mediated inhibition of calcium release channel inositol 1,4,5-trisphosphate receptor subtype 3 blocks glioblastoma invasion and extends survival, Cancer Res. 70 (2010) 1173–1183.
[73] T. Tsunoda, H. Koga, A. Yokomizo, K. Tatsugami, M. Eto, J. Inokuchi, A. Hirata, K. Masuda, K. Okumura, S. Naito, Inositol 1,4,5-trisphosphate (IP3) receptor type1 (IP3R1) modulates the acquisition of cisplatin resistance in bladder cancer cell lines, Oncogene 24 (2005) 1396–1402.
[74] C.K. Min, D.R. Yeom, K.E. Lee, H.K. Kwon, M. Kang, Y.S. Kim, Z.Y. Park, H. Jeon, H. Kim do, Coupling of ryanodine receptor 2 and voltage-dependent anion channel 2 is essential for Ca(2)+ transfer from the sarcoplasmic reticulum to the mitochondria in the heart, Biochem. J. 447 (2012) 371–379.
[75] G. Hajnoczky, G. Csordas, M. Madesh, P. Pacher, Control of apoptosis by IP(3) and ryanodine receptor driven calcium signals, Cell Calcium 28 (2000) 349–363.
[76] G. Hajnoczky, G. Csordas, M. Yi, Old players in a new role: mitochondria-associated membranes, VDAC, and ryanodine receptors as contributors to calcium signal propagation from endoplasmic reticulum to the mitochondria, Cell Calcium 32 (2002) 363–377.
[77] B.C. Kim, H.T. Kim, M. Mamura, I.S. Ambudkar, K.S. Choi, S.J. Kim, Tumor necrosis factor induces apoptosis in hepatoma cells by increasing Ca(2+) release from the endoplasmic reticulum and suppressing Bcl-2 expression, J. Biol. Chem. 277 (2002) 31381–31389.
[78] D.S. Luciani, K.S. Gwiazda, T.L. Yang, T.B. Kalynyak, Y. Bychkivska, M.H. Frey, K.D. Jeffrey, A.V. Sampaio, T.M. Underhill, J.D. Johnson, Roles of IP3R and RyR Ca2+ channels in endoplasmic reticulum stress and beta-cell death, Diabetes 58 (2009) 422–432.
[79] A. Ruiz, C. Matute, E. Alberdi, Endoplasmic reticulum Ca(2+) release through ryanodine and IP(3) receptors contributes to neuronal excitotoxicity, Cell Calcium 46 (2009) 273–281.
[80] T. Vervliet, E. Decrock, J. Molgo, V. Sorrentino, L. Missiaen, L. Leybaert, H. De Smedt, N.N. Kasri, J.B. Parys, G. Bultynck, Bcl-2 binds to and inhibits ryanodine receptors, J. Cell Sci. 127 (2014) 2782–2792.
[81] J.M. Baughman, F. Perocchi, H.S. Girgis, M. Plovanich, C.A. Belcher-Timme, Y. Sancak, X.R. Bao, L. Strittmatter, O. Goldberger, R.L. Bogorad, V. Koteliansky, V.K. Mootha, Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter, Nature 476 (2011) 341–345.
[82] D. De Stefani, A. Raffaello, E. Teardo, I. Szabo, R. Rizzuto, A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter, Nature 476 (2011) 336–340.
[83] S. Marchi, L. Lupini, S. Patergnani, A. Rimessi, S. Missiroli, M. Bonora, A. Bononi, F. Corra, C. Giorgi, E. De Marchi, F. Poletti, R. Gafa, G. Lanza, M. Negrini, R. Rizzuto, P. Pinton, Downregulation of the mitochondrial calcium uniporter by cancer-related miR-25, Curr. Biol. 23 (2013) 58–63.
[84] M.C. Curry, A.A. Peters, P.A. Kenny, S.J. Roberts-Thomson, G.R. Monteith, Mitochondrial calcium uniporter silencing potentiates caspase-independent cell death in MDA-MB-231 breast cancer cells, Biochem. Biophys. Res. Commun. 434 (2013) 695–700.
[85] X. Pan, J. Liu, T. Nguyen, C. Liu, J. Sun, Y. Teng, M.M. Fergusson, I.I. Rovira, M. Allen, D.A. Springer, A.M. Aponte, M. Gucek, R.S. Balaban, E. Murphy, T. Finkel, The physiological role of mitochondrial calcium revealed by mice lacking the mitochondrial calcium uniporter, Nat. Cell Biol. 15 (2013) 1464–1472.
[86] S. Herzig, K. Maundrell, J.C. Martinou, Life without the mitochondrial calcium uniporter, Nat. Cell Biol. 15 (2013) 1398–1400.
[87] K.N. Alavian, G. Beutner, E. Lazrove, S. Sacchetti, H.A. Park, P. Licznerski, H. Li, P. Nabili, K. Hockensmith, M. Graham, G.A. Porter Jr., E.A. Jonas, An uncoupling channel within the c-subunit ring of the F1FO ATP synthase is the mitochondrial permeability transition pore, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 10580–10585.
[88] M. Bonora, M.R. Wieckowski, C. Chinopoulos, O. Kepp, G. Kroemer, L. Galluzzi, P. Pinton, Molecular mechanisms of cell death: central implication of ATP synthase in mitochondrial permeability transition, Oncogene 0 (2014).
[89] V. Giorgio, S. von Stockum, M. Antoniel, A. Fabbro, F. Fogolari, M. Forte, G.D. Glick, V. Petronilli, M. Zoratti, I. Szabo, G. Lippe, P. Bernardi, Dimers of mitochondrial ATP synthase form the permeability transition pore, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 5887–5892.
[90] V. Shoshan-Barmatz, D. Gincel, The voltage-dependent anion channel: characterization, modulation, and role in mitochondrial function in cell life and death, Cell Biochem. Biophys. 39 (2003) 279–292.
[91] Y. Zheng, Y. Shi, C. Tian, C. Jiang, H. Jin, J. Chen, A. Almasan, H. Tang, Q. Chen, Essential role of the voltage-dependent anion channel (VDAC) in mitochondrial permeability transition pore opening and cytochrome c release induced by arsenic trioxide, Oncogene 23 (2004) 1239–1247.
[92] C.P. Baines, R.A. Kaiser, T. Sheiko, W.J. Craigen, J.D. Molkentin, Voltage-dependent anion channels are dispensable for mitochondrial-dependent cell death, Nat. Cell Biol. 9 (2007) 550–555.
[93] T.K. Rostovtseva, S.M. Bezrukov, VDAC regulation: role of cytosolic proteins and mitochondrial lipids, J. Bioenerg. Biomembr. 40 (2008) 163–170.
[94] N. Tajeddine, L. Galluzzi, O. Kepp, E. Hangen, E. Morselli, L. Senovilla, N. Araujo, G. Pinna, N. Larochette, N. Zamzami, N. Modjtahedi, A. Harel-Bellan, G. Kroemer, Hierarchical involvement of Bak, VDAC1 and Bax in cisplatin-induced cell death, Oncogene 27 (2008) 4221–4232.
[95] E.H. Cheng, T.V. Sheiko, J.K. Fisher, W.J. Craigen, S.J. Korsmeyer, VDAC2 inhibits BAK activation and mitochondrial apoptosis, Science 301 (2003) 513–517.
[96] W. Tan, M. Colombini, VDAC closure increases calcium ion flux, Biochim. Biophys. Acta 1768 (2007) 2510–2515.
[97] M.G. Vander Heiden, N.S. Chandel, X.X. Li, P.T. Schumacker, M. Colombini, C.B. Thompson, Outer mitochondrial membrane permeability can regulate coupled respiration and cell survival, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 4666–4671.
[98] E. Rapizzi, P. Pinton, G. Szabadkai, M.R. Wieckowski, G. Vandecasteele, G. Baird, R.A. Tuft, K.E. Fogarty, R. Rizzuto, Recombinant expression of the voltage-dependent anion channel enhances the transfer of Ca2+ microdomains to mitochondria, J. Cell Biol. 159 (2002) 613–624.
[99] G. Szabadkai, K. Bianchi, P. Varnai, D. De Stefani, M.R. Wieckowski, D. Cavagna, A.I. Nagy, T. Balla, R. Rizzuto, Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels, J. Cell Biol. 175 (2006) 901–911.
[100] D. De Stefani, A. Bononi, A. Romagnoli, A. Messina, V. De Pinto, P. Pinton, R. Rizzuto, VDAC1 selectively transfers apoptotic Ca2+ signals to mitochondria, Cell Death Differ. 19 (2012) 267–273.
[101] J.T. Smyth, S.Y. Hwang, T. Tomita, W.I. DeHaven, J.C. Mercer, J.W. Putney, Activation and regulation of store-operated calcium entry, J. Cell. Mol. Med. 14 (2010) 2337–2349.
[102] M. Prakriya, S. Feske, Y. Gwack, S. Srikanth, A. Rao, P.G. Hogan, Orai1 is an essential pore subunit of the CRAC channel, Nature 443 (2006) 230–233.
[103] S.L. Zhang, Y. Yu, J. Roos, J.A. Kozak, T.J. Deerinck, M.H. Ellisman, K.A. Stauderman, M.D. Cahalan, STIM1 is a Ca2+ sensor that activates CRAC channels and migrates from the Ca2+ store to the plasma membrane, Nature 437 (2005) 902–905.
[104] A.B. Parekh, J.W. Putney Jr., Store-operated calcium channels, Physiol. Rev. 85 (2005) 757–810.
[105] N. Prevarskaya, R. Skryma, Y. Shuba, Targeting Ca(2)(+) transport in cancer: close reality or long perspective? Expert Opin. Ther. Targets 17 (2013) 225–241.
[106] M. Flourakis, V. Lehen'kyi, B. Beck, M. Raphael, M. Vandenberghe, F.V. Abeele, M. Roudbaraki, G. Lepage, B. Mauroy, C. Romanin, Y. Shuba, R. Skryma, N. Prevarskaya, Orai1 contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells, Cell Death Dis. 1 (2010) e75.
[107] N. Henke, P. Albrecht, I. Bouchachia, M. Ryazantseva, K. Knoll, J. Lewerenz, E. Kaznacheyeva, P. Maher, A. Methner, The plasma membrane channel ORAI1 mediates detrimental calcium influx caused by endogenous oxidative stress, Cell Death Dis. 4 (2013) e470.

[108] N. Khadra, L. Bresson-Bepoldin, A. Penna, B. Chaigne-Delalande, B. Segui, T. Levade, A.M. Vacher, J. Reiffers, T. Ducret, J.F. Moreau, M.D. Cahalan, P. Vacher, P. Legembre, CD95 triggers Orai1-mediated localized Ca2 + entry, regulates recruitment of protein kinase C (PKC) beta2, and prevents death-inducing signaling complex formation, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 19072–19077.
[109] K. Kondratska, A. Kondratskyi, M. Yassine, L. Lemonnier, G. Lepage, A. Morabito, R. Skryma, N. Prevarskaya, Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma, Biochim. Biophys. Acta 1843 (2014) 2263–2269.
[110] W. Li, M. Zhang, L. Xu, D. Lin, S. Cai, F. Zou, The apoptosis of non-small cell lung cancer induced by cisplatin through modulation of STIM1, Exp. Toxicol. Pathol. 65 (2013) 1073–1081.
[111] H. Liu, J.D. Hughes, S. Rollins, B. Chen, E. Perkins, Calcium entry via ORAI1 regulates glioblastoma cell proliferation and apoptosis, Exp. Mol. Pathol. 91 (2011) 753–760.
[112] W. Rao, L. Zhang, N. Su, K. Wang, H. Hui, L. Wang, T. Chen, P. Luo, Y.F. Yang, Z.B. Liu, Z. Fei, Blockade of SOCE protects HT22 cells from hydrogen peroxide-induced apoptosis, Biochem. Biophys. Res. Commun. 441 (2013) 351–356.
[113] S. Schmidt, G. Liu, W. Yang, S. Honisch, S. Pantelakos, C. Stournaras, A. Honig, F. Lang, Enhanced Orai1 and STIM1 expression as well as store operated Ca2 + entry in therapy resistant ovary carcinoma cells, Oncotarget 5 (2014) 4799–4810.
[114] W.I. DeHaven, J.T. Smyth, R.R. Boyles, J.W. Putney Jr., Calcium inhibition and calcium potentiation of Orai1, Orai2, and Orai3 calcium release-activated calcium channels, J. Biol. Chem. 282 (2007) 17548–17556.
[115] M. Hoth, B.A. Niemeyer, The neglected CRAC proteins: Orai2, Orai3, and STIM2, Curr. Top. Membr. 71 (2013) 237–271.
[116] B. Nilius, TRP channels in disease, Biochim. Biophys. Acta 1772 (2007) 805–812.
[117] G. Shapovalov, V. Lehen'kyi, R. Skryma, N. Prevarskaya, TRP channels in cell survival and cell death in normal and transformed cells, Cell Calcium 50 (2011) 295–302.
[118] A.L. Perraud, A. Fleig, C.A. Dunn, L.A. Bagley, P. Launay, C. Schmitz, A.J. Stokes, Q. Zhu, M.J. Bessman, R. Penner, J.P. Kinet, A.M. Scharenberg, ADP-ribose gating of the calcium-permeable LTRPC2 channel revealed by Nudix motif homology, Nature 411 (2001) 595–599.
[119] J. Wehrhahn, R. Kraft, C. Harteneck, S. Hauschildt, Transient receptor potential melastatin 2 is required for lipopolysaccharide-induced cytokine production in human monocytes, J. Immunol. 184 (2010) 2386–2393.
[120] Y. Hara, M. Wakamori, M. Ishii, E. Maeno, M. Nishida, T. Yoshida, H. Yamada, S. Shimizu, E. Mori, J. Kudoh, N. Shimizu, H. Kurose, Y. Okada, K. Imoto, Y. Mori, LTRPC2 Ca2 +-permeable channel activated by changes in redox status confers susceptibility to cell death, Mol. Cell 9 (2002) 163–173.
[121] U. Orfanelli, E. Jachetti, F. Chiacchiera, M. Grioni, P. Brambilla, A. Briganti, M. Freschi, F. Martinelli-Boneschi, C. Doglioni, F. Montorsi, M. Bellone, G. Casari, D. Pasini, G. Lavorgna, Antisense transcription at the TRPM2 locus as a novel prognostic marker and therapeutic target in prostate cancer, Oncogene (2014).
[122] U. Orfanelli, A.K. Wenke, C. Doglioni, V. Russo, A.K. Bosserhoff, G. Lavorgna, Identification of novel sense and antisense transcription at the TRPM2 locus in cancer, Cell Res. 18 (2008) 1128–1140.
[123] L.W. Runnels, L. Yue, D.E. Clapham, TRP-PLIK, a bifunctional protein with kinase and ion channel activities, Science 291 (2001) 1043–1047.
[124] L.V. Ryazanova, L.J. Rondon, S. Zierler, Z. Hu, J. Galli, T.P. Yamaguchi, A. Mazur, A. Fleig, A.G. Ryazanov, TRPM7 is essential for Mg(2 +) homeostasis in mammals, Nat. Commun. 1 (2010) 109.
[125] N.M. Ng, S.P. Jiang, Z.Q. Lv, Retrovirus-mediated siRNA targeting TRPM7 gene induces apoptosis in RBL-2H3 cells, Eur. Rev. Med. Pharmacol. Sci. 16 (2012) 1172–1178.
[126] R.C. Wykes, M. Lee, S.M. Duffy, W. Yang, E.P. Seward, P. Bradding, Functional transient receptor potential melastatin 7 channels are critical for human mast cell survival, J. Immunol. 179 (2007) 4045–4052.
[127] M.J. Nadler, M.C. Hermosura, K. Inabe, A.L. Perraud, Q. Zhu, A.J. Stokes, T. Kurosaki, J.P. Kinet, R. Penner, A.M. Scharenberg, A. Fleig, LTRPC7 is a Mg.ATP-regulated divalent cation channel required for cell viability, Nature 411 (2001) 590–595.
[128] B.J. Kim, E.J. Park, J.H. Lee, J.H. Jeon, S.J. Kim, I. So, Suppression of transient receptor potential melastatin 7 channel induces cell death in gastric cancer, Cancer Sci. 99 (2008) 2502–2509.
[129] B.N. Desai, G. Krapivinsky, B. Navarro, L. Krapivinsky, B.C. Carter, S. Febvay, M. Delling, A. Penumaka, I.S. Ramsey, Y. Manasian, D.E. Clapham, Cleavage of TRPM7 releases the kinase domain from the ion channel and regulates its participation in Fas-induced apoptosis, Dev. Cell 22 (2012) 1149–1162.
[130] D.D. McKemy, W.M. Neuhausser, D. Julius, Identification of a cold receptor reveals a general role for TRP channels in thermosensation, Nature 416 (2002) 52–58.
[131] A.M. Peier, A. Moqrich, A.C. Hergarden, A.J. Reeve, D.A. Andersson, G.M. Story, T.J. Earley, I. Dragoni, P. McIntyre, S. Bevan, A. Patapoutian, A TRP channel that senses cold stimuli and menthol, Cell 108 (2002) 705–715.
[132] L. Tsavaler, M.H. Shapero, S. Morkowski, R. Laus, Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins, Cancer Res. 61 (2001) 3760–3769.
[133] G. Bidaux, M. Flourakis, S. Thebault, A. Zholos, B. Beck, D. Gkika, M. Roudbaraki, J.L. Bonnal, B. Mauroy, Y. Shuba, R. Skryma, N. Prevarskaya, Prostate cell differentiation status determines transient receptor potential melastatin member 8 channel subcellular localization and function, J. Clin. Invest. 117 (2007) 1647–1657.
[134] S. Thebault, L. Lemonnier, G. Bidaux, M. Flourakis, A. Bavencoffe, D. Gordienko, M. Roudbaraki, P. Delcourt, Y. Panchin, Y. Shuba, R. Skryma, N. Prevarskaya, Novel role of cold/menthol-sensitive transient receptor potential melastatine family member 8 (TRPM8) in the activation of store-operated channels in LNCaP human prostate cancer epithelial cells, J. Biol. Chem. 280 (2005) 39423–39435.
[135] L. Zhang, G.J. Barritt, Evidence that TRPM8 is an androgen-dependent Ca2 + channel required for the survival of prostate cancer cells, Cancer Res. 64 (2004) 8365–8373.
[136] H. Yamamura, S. Ugawa, T. Ueda, A. Morita, S. Shimada, TRPM8 activation suppresses cellular viability in human melanoma, Am. J. Physiol. Cell Physiol. 295 (2008) C296–301.
[137] Q. Li, X. Wang, Z. Yang, B. Wang, S. Li, Menthol induces cell death via the TRPM8 channel in the human bladder cancer cell line T24, Oncology 77 (2009) 335–341.
[138] S. Zhu, Y. Wang, L. Pan, S. Yang, Y. Sun, X. Wang, F. Hu, Involvement of transient receptor potential melastatin-8 (TRPM8) in menthol-induced calcium entry, reactive oxygen species production and cell death in rheumatoid arthritis rat synovial fibroblasts, Eur. J. Pharmacol. 725 (2014) 1–9.
[139] Y. Wang, Z. Yang, Z. Meng, H. Cao, G. Zhu, T. Liu, X. Wang, Knockdown of TRPM8 suppresses cancer malignancy and enhances epirubicin-induced apoptosis in human osteosarcoma cells, Int. J. Biol. Sci. 10 (2013) 90–102.
[140] M.J. Caterina, M.A. Schumacher, M. Tominaga, T.A. Rosen, J.D. Levine, D. Julius, The capsaicin receptor: a heat-activated ion channel in the pain pathway, Nature 389 (1997) 816–824.
[141] C. Amantini, M. Mosca, M. Nabissi, R. Lucciarini, S. Caprodossi, A. Arcella, F. Giangaspero, G. Santoni, Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation, J. Neurochem. 102 (2007) 977–990.
[142] A.M. Bode, Y.Y. Cho, D. Zheng, F. Zhu, M.E. Ericson, W.Y. Ma, K. Yao, Z. Dong, Transient receptor potential type vanilloid 1 suppresses skin carcinogenesis, Cancer Res. 69 (2009) 905–913.
[143] X. Miao, G. Liu, X. Xu, C. Xie, F. Sun, Y. Yang, T. Zhang, S. Hua, W. Fan, Q. Li, S. Huang, Q. Wang, D. Zhong, High expression of vanilloid receptor-1 is associated with better prognosis of patients with hepatocellular carcinoma, Cancer Genet. Cytogenet. 186 (2008) 25–32.
[144] C. Amantini, P. Ballarini, S. Caprodossi, M. Nabissi, M.B. Morelli, R. Lucciarini, M.A. Cardarelli, G. Mammana, G. Santoni, Triggering of transient receptor potential vanilloid type 1 (TRPV1) by capsaicin induces Fas/CD95-mediated apoptosis of urothelial cancer cells in an ATM-dependent manner, Carcinogenesis 30 (2009) 1320–1329.
[145] K. Stock, J. Kumar, M. Synowitz, S. Petrosino, R. Imperatore, E.S. Smith, P. Wend, B. Purfurst, U.A. Nuber, U. Gurok, V. Matyash, J.H. Walzlein, S.R. Chirasani, G. Dittmar, B.F. Cravatt, S. Momma, G.R. Lewin, A. Ligresti, L. De Petrocellis, L. Cristino, V. Di Marzo, H. Kettenmann, R. Glass, Neural precursor cells induce cell death of high-grade astrocytomas through stimulation of TRPV1, Nat. Med. 18 (2012) 1232–1238.
[146] H. Shirakawa, T. Yamaoka, K. Sanpei, H. Sasaoka, T. Nakagawa, S. Kaneko, TRPV1 stimulation triggers apoptotic cell death of rat cortical neurons, Biochem. Biophys. Res. Commun. 377 (2008) 1211–1215.
[147] J.K. Lau, K.C. Brown, A.M. Dom, T.R. Witte, B.A. Thornhill, C.M. Crabtree, H.E. Perry, J.M. Brown, J.G. Ball, R.G. Creel, C.L. Damron, W.D. Rollyson, C.D. Stevenson, W.E. Hardman, M.A. Valentovic, A.B. Carpenter, P. Dasgupta, Capsaicin induces apoptosis in human small cell lung cancer via the TRPV6 receptor and the calpain pathway, Apoptosis 19 (2014) 1190–1201.
[148] J. Chow, M. Norng, J. Zhang, J. Chai, TRPV6 mediates capsaicin-induced apoptosis in gastric cancer cells—mechanisms behind a possible new "hot" cancer treatment, Biochim. Biophys. Acta 1773 (2007) 565–576.
[149] A. Athanasiou, P.A. Smith, S. Vakilpour, N.M. Kumaran, A.E. Turner, D. Bagiokou, R. Layfield, D.E. Ray, A.D. Westwell, S.P. Alexander, D.A. Kendall, D.N. Lobo, S.A. Watson, A. Lophatanon, K.A. Muir, D.A. Guo, T.E. Bates, Vanilloid receptor agonists and antagonists are mitochondrial inhibitors: how vanilloids cause non-vanilloid receptor mediated cell death, Biochem. Biophys. Res. Commun. 354 (2007) 50–55.
[150] M.J. Caterina, T.A. Rosen, M. Tominaga, A.J. Brake, D. Julius, A capsaicin-receptor homologue with a high threshold for noxious heat, Nature 398 (1999) 436–441.
[151] V. Lehen'kyi, N. Prevarskaya, TRPV2 (transient receptor potential cation channel, subfamily V, member 2), Atlas Genet. Cytogenet. Oncol. Haematol. 16 (8) (2012) 563–567.
[152] M. Nabissi, M.B. Morelli, C. Amantini, V. Farfariello, L. Ricci-Vitiani, S. Caprodossi, A. Arcella, M. Santoni, F. Giangaspero, R. De Maria, G. Santoni, TRPV2 channel negatively controls glioma cell proliferation and resistance to Fas-induced apoptosis in ERK-dependent manner, Carcinogenesis 31 (2010) 794–803.
[153] M. Nabissi, M.B. Morelli, M. Santoni, G. Santoni, Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents, Carcinogenesis 34 (2013) 48–57.
[154] T. Yamada, T. Ueda, Y. Shibata, Y. Ikegami, M. Saito, Y. Ishida, S. Ugawa, K. Kohri, S. Shimada, TRPV2 activation induces apoptotic cell death in human T24 bladder cancer cells: a potential therapeutic target for bladder cancer, Urology 76 (2010) (509 e501-507).
[155] M. Monet, V. Lehen'kyi, F. Gackiere, V. Firlej, M. Vandenberghe, M. Roudbaraki, D. Gkika, A. Pourtier, G. Bidaux, C. Slomianny, P. Delcourt, F. Rassendren, J.P. Bergerat, J. Ceraline, F. Cabon, S. Humez, N. Prevarskaya, Role of cationic channel TRPV2 in promoting prostate cancer migration and progression to androgen resistance, Cancer Res. 70 (2010) 1225–1235.
[156] V. Lehen'kyi, M. Raphael, N. Prevarskaya, The role of the TRPV6 channel in cancer, J. Physiol. 590 (2012) 1369–1376.
[157] J.B. Peng, L. Zhuang, U.V. Berger, R.M. Adam, B.J. Williams, E.M. Brown, M.A. Hediger, M.R. Freeman, CaT1 expression correlates with tumor grade in prostate cancer, Biochem. Biophys. Res. Commun. 282 (2001) 729–734.
[158] V. Lehen'kyi, M. Flourakis, R. Skryma, N. Prevarskaya, TRPV6 channel controls prostate cancer cell proliferation via Ca(2 +)/NFAT-dependent pathways, Oncogene 26 (2007) 7380–7385.

[159] S. Peleg, J.H. Sellin, Y. Wang, M.R. Freeman, S. Umar, Suppression of aberrant transient receptor potential cation channel, subfamily V, member 6 expression in hyperproliferative colonic crypts by dietary calcium, Am. J. Physiol. Gastrointest. Liver Physiol. 299 (2010) G593–601.
[160] E. Madan, R. Gogna, B. Keppler, U. Pati, p53 increases intra-cellular calcium release by transcriptional regulation of calcium channel TRPC6 in GaQ3-treated cancer cells, PLoS One 8 (2013) e71016.
[161] H. Yang, B. Zhao, C. Liao, R. Zhang, K. Meng, J. Xu, J. Jiao, High glucose-induced apoptosis in cultured podocytes involves TRPC6-dependent calcium entry via the RhoA/ROCK pathway, Biochem. Biophys. Res. Commun. 434 (2013) 394–400.
[162] C. Ingueneau, U.D. Huynh, B. Marcheix, A. Athias, P. Gambert, A. Negre-Salvayre, R. Salvayre, C. Vindis, TRPC1 is regulated by caveolin-1 and is involved in oxidized LDL-induced apoptosis of vascular smooth muscle cells, J. Cell. Mol. Med. 13 (2009) 1620–1631.
[163] B.S. Marasa, L. Xiao, J.N. Rao, T. Zou, L. Liu, J. Wang, E. Bellavance, D.J. Turner, J.Y. Wang, Induced TRPC1 expression increases protein phosphatase 2A sensitizing intestinal epithelial cells to apoptosis through inhibition of NF-kappaB activation, Am. J. Physiol. Cell Physiol. 294 (2008) C1277–1287.
[164] S. Bollimuntha, M. Ebadi, B.B. Singh, TRPC1 protects human SH-SY5Y cells against salsolinol-induced cytotoxicity by inhibiting apoptosis, Brain Res. 1099 (2006) 141–149.
[165] E.A. Schaefer, S. Stohr, M. Meister, A. Aigner, T. Gudermann, T.R. Buech, Stimulation of the chemosensory TRPA1 cation channel by volatile toxic substances promotes cell survival of small cell lung cancer cells, Biochem. Pharmacol. 85 (2013) 426–438.
[166] T. Wegierski, D. Steffl, C. Kopp, R. Tauber, B. Buchholz, R. Nitschke, E.W. Kuehn, G. Walz, M. Kottgen, TRPP2 channels regulate apoptosis through the Ca2+ concentration in the endoplasmic reticulum, EMBO J. 28 (2009) 490–499.
[167] M. Xu, X. Li, S.W. Walsh, Y. Zhang, J.M. Abais, K.M. Boini, P.L. Li, Intracellular two-phase Ca2+ release and apoptosis controlled by TRP-ML1 channel activity in coronary arterial myocytes, Am. J. Physiol. Cell Physiol. 304 (2013) C458–466.
[168] C. Grimm, S. Jors, S. Heller, Life and death of sensory hair cells expressing constitutively active TRPML3, J. Biol. Chem. 284 (2009) 13823–13831.
[169] S. Lev, D.A. Zeevi, A. Frumkin, V. Offen-Glasner, G. Bach, B. Minke, Constitutive activity of the human TRPML2 channel induces cell degeneration, J. Biol. Chem. 285 (2010) 2771–2782.
[170] W.A. Catterall, Voltage-gated calcium channels, Cold Spring Harb. Perspect. Biol. 3 (2011) a003947.
[171] L. Lacinova, Voltage-dependent calcium channels, Gen. Physiol. Biophys. 24 (Suppl. 1) (2005) 1–78.
[172] M.F. Cano-Abad, M. Villarroya, A.G. Garcia, N.H. Gabilan, M.G. Lopez, Calcium entry through L-type calcium channels causes mitochondrial disruption and chromaffin cell death, J. Biol. Chem. 276 (2001) 39695–39704.
[173] N. Diaz-Prieto, I. Herrera-Peco, A.M. de Diego, A. Ruiz-Nuno, S. Gallego-Sandin, M.G. Lopez, A.G. Garcia, M.F. Cano-Abad, Bcl2 mitigates Ca2+ entry and mitochondrial Ca2+ overload through downregulation of L-type Ca2+ channels in PC12 cells, Cell Calcium 44 (2008) 339–352.
[174] L. Juntti-Berggren, O. Larsson, P. Rorsman, C. Ammala, K. Bokvist, K. Wahlander, P. Nicotera, J. Dypbukt, S. Orrenius, A. Hallberg, et al., Increased activity of L-type Ca2+ channels exposed to serum from patients with type I diabetes, Science 261 (1993) 86–90.
[175] L. Wang, A. Bhattacharjee, Z. Zuo, F. Hu, R.E. Honkanen, P.O. Berggren, M. Li, A low voltage-activated Ca2+ current mediates cytokine-induced pancreatic beta-cell death, Endocrinology 140 (1999) 1200–1204.
[176] B. Dziegielewska, D.L. Brautigan, J.M. Larner, J. Dziegielewski, T-type Ca2+ channel inhibition induces p53-dependent cell growth arrest and apoptosis through activation of p38-MAPK in colon cancer cells, Mol. Cancer Res. 12 (2014) 348–358.
[177] A. Das, C. Pushparaj, J. Herreros, M. Nager, R. Vilella, M. Portero, R. Pamplona, X. Matias-Guiu, R.M. Marti, C. Canti, T-type calcium channel blockers inhibit autophagy and promote apoptosis of malignant melanoma cells, Pigment Cell Melanoma Res. 26 (2013) 874–885.
[178] N.C. Valerie, B. Dziegielewska, A.S. Hosing, E. Augustin, L.S. Gray, D.L. Brautigan, J.M. Larner, J. Dziegielewski, Inhibition of T-type calcium channels disrupts Akt signaling and promotes apoptosis in glioblastoma cells, Biochem. Pharmacol. 85 (2013) 888–897.
[179] D.P. Mishra, R. Pal, C. Shaha, Changes in cytosolic Ca2+ levels regulate Bcl-xS and Bcl-xL expression in spermatogenic cells during apoptotic death, J. Biol. Chem. 281 (2006) 2133–2143.
[180] B. Dziegielewska, L.S. Gray, J. Dziegielewski, T-type calcium channels blockers as new tools in cancer therapies, Pflugers Arch. 466 (2014) 801–810.
[181] C.D. Bortner, J.A. Cidlowski, Cell shrinkage and monovalent cation fluxes: role in apoptosis, Arch. Biochem. Biophys. 462 (2007) 176–188.
[182] C.D. Bortner, F.M. Hughes Jr., J.A. Cidlowski, A primary role for K+ and Na+ efflux in the activation of apoptosis, J. Biol. Chem. 272 (1997) 32436–32442.
[183] K. Cain, C. Langlais, X.M. Sun, D.G. Brown, G.M. Cohen, Physiological concentrations of K+ inhibit cytochrome c-dependent formation of the apoptosome, J. Biol. Chem. 276 (2001) 41985–41990.
[184] F.M. Hughes Jr., C.D. Bortner, G.D. Purdy, J.A. Cidlowski, Intracellular K+ suppresses the activation of apoptosis in lymphocytes, J. Biol. Chem. 272 (1997) 30567–30576.
[185] S. Krick, O. Platoshyn, M. Sweeney, H. Kim, J.X. Yuan, Activation of K+ channels induces apoptosis in vascular smooth muscle cells, Am. J. Physiol. Cell Physiol. 280 (2001) C970–979.
[186] H. Nadeau, S. McKinney, D.J. Anderson, H.A. Lester, ROMK1 (Kir1.1) causes apoptosis and chronic silencing of hippocampal neurons, J. Neurophysiol. 84 (2000) 1062–1075.
[187] S.P. Yu, C.H. Yeh, S.L. Sensi, B.J. Gwag, L.M. Canzoniero, Z.S. Farhangrazi, H.S. Ying, M. Tian, L.L. Dugan, D.W. Choi, Mediation of neuronal apoptosis by enhancement of outward potassium current, Science 278 (1997) 114–117.
[188] G.J. Thompson, C. Langlais, K. Cain, E.C. Conley, G.M. Cohen, Elevated extracellular [K+] inhibits death-receptor- and chemical-mediated apoptosis prior to caspase activation and cytochrome c release, Biochem. J. 357 (2001) 137–145.
[189] C.C. Shieh, M. Coghlan, J.P. Sullivan, M. Gopalakrishnan, Potassium channels: molecular defects, diseases, and therapeutic opportunities, Pharmacol. Rev. 52 (2000) 557–594.
[190] Z. Wang, Roles of K+ channels in regulating tumour cell proliferation and apoptosis, Pflugers Arch. 448 (2004) 274–286.
[191] E.D. Burg, C.V. Remillard, J.X. Yuan, K+ channels in apoptosis, J. Membr. Biol. 209 (2006) 3–20.
[192] L.A. Pardo, W. Stuhmer, The roles of K(+) channels in cancer, Nat. Rev. Cancer 14 (2014) 39–48.
[193] S.P. Yu, Regulation and critical role of potassium homeostasis in apoptosis, Prog. Neurobiol. 70 (2003) 363–386.
[194] I. Szabo, M. Zoratti, E. Gulbins, Contribution of voltage-gated potassium channels to the regulation of apoptosis, FEBS Lett. 584 (2010) 2049–2056.
[195] S. Pal, K.A. Hartnett, J.M. Nerbonne, E.S. Levitan, E. Aizenman, Mediation of neuronal apoptosis by Kv2.1-encoded potassium channels, J. Neurosci. 23 (2003) 4798–4802.
[196] M.B. McFerrin, K.L. Turner, V.A. Cuddapah, H. Sontheimer, Differential role of IK and BK potassium channels as mediators of intrinsic and extrinsic apoptotic cell death, Am. J. Physiol. Cell Physiol. 303 (2012) C1070–1078.
[197] M.C. McCord, E. Aizenman, Convergent Ca2+ and Zn2+ signaling regulates apoptotic Kv2.1 K+ currents, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 13988–13993.
[198] P.T. Redman, K. He, K.A. Hartnett, B.S. Jefferson, L. Hu, P.A. Rosenberg, E.S. Levitan, E. Aizenman, Apoptotic surge of potassium currents is mediated by p38 phosphorylation of Kv2.1, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 3568–3573.
[199] S. Krick, O. Platoshyn, M. Sweeney, S.S. McDaniel, S. Zhang, L.J. Rubin, J.X. Yuan, Nitric oxide induces apoptosis by activating K+ channels in pulmonary vascular smooth muscle cells, Am. J. Physiol. Heart Circ. Physiol. 282 (2002) H184–193.
[200] H.H. Nietsch, M.W. Roe, J.F. Fiekers, A.L. Moore, S.D. Lidofsky, Activation of potassium and chloride channels by tumor necrosis factor alpha. Role in liver cell death, J. Biol. Chem. 275 (2000) 20556–20561.
[201] H. Wang, Y. Zhang, L. Cao, H. Han, J. Wang, B. Yang, S. Nattel, Z. Wang, HERG K+ channel, a regulator of tumor cell apoptosis and proliferation, Cancer Res. 62 (2002) 4843–4848.
[202] A.J. Patel, M. Lazdunski, The 2P-domain K+ channels: role in apoptosis and tumorigenesis, Pflugers Arch. 448 (2004) 261–273.
[203] M.F. El Hachmane, K.A. Rees, E.L. Veale, V.V. Sumbayev, A. Mathie, Enhancement of TWIK-related acid-sensitive potassium channel 3 (TASK3) two-pore domain potassium channel activity by tumor necrosis factor alpha, J. Biol. Chem. 289 (2014) 1388–1401.
[204] I. Lauritzen, M. Zanzouri, E. Honore, F. Duprat, M.U. Ehrengruber, M. Lazdunski, A.J. Patel, K+-dependent cerebellar granule neuron apoptosis. Role of task leak K+ channels, J. Biol. Chem. 278 (2003) 32068–32076.
[205] J.R. Trimarchi, L. Liu, P.J. Smith, D.L. Keefe, Apoptosis recruits two-pore domain potassium channels used for homeostatic volume regulation, Am. J. Physiol. Cell Physiol. 282 (2002) C588–594.
[206] O. Platoshyn, S. Zhang, S.S. McDaniel, J.X. Yuan, Cytochrome c activates K+ channels before inducing apoptosis, Am. J. Physiol. Cell Physiol. 283 (2002) C1298–1305.
[207] D. Ekhterae, O. Platoshyn, S. Krick, Y. Yu, S.S. McDaniel, J.X. Yuan, Bcl-2 decreases voltage-gated K+ channel activity and enhances survival in vascular smooth muscle cells, Am. J. Physiol. Cell Physiol. 281 (2001) C157–165.
[208] L. Leanza, M. Zoratti, E. Gulbins, I. Szabo, Mitochondrial ion channels as oncological targets, Oncogene (2014).
[209] I. Szabo, L. Leanza, E. Gulbins, M. Zoratti, Physiology of potassium channels in the inner membrane of mitochondria, Pflugers Arch. 463 (2012) 231–246.
[210] I. Szabo, J. Bock, H. Grassme, M. Soddemann, B. Wilker, F. Lang, M. Zoratti, E. Gulbins, Mitochondrial potassium channel Kv1.3 mediates Bax-induced apoptosis in lymphocytes, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14861–14866.
[211] L. Leanza, M. Zoratti, E. Gulbins, I. Szabo, Induction of apoptosis in macrophages via Kv1.3 and Kv1.5 potassium channels, Curr. Med. Chem. 19 (2012) 5394–5404.
[212] L. Leanza, B. Henry, N. Sassi, M. Zoratti, K.G. Chandy, E. Gulbins, I. Szabo, Inhibitors of mitochondrial Kv1.3 channels induce Bax/Bak-independent death of cancer cells, EMBO Mol. Med. 4 (2012) 577–593.
[213] L. Leanza, L. Trentin, K.A. Becker, F. Frezzato, M. Zoratti, G. Semenzato, E. Gulbins, I. Szabo, Clofazimine, Psora-4 and PAP-1, inhibitors of the potassium channel Kv1.3, as a new and selective therapeutic strategy in chronic lymphocytic leukemia, Leukemia 27 (2013) 1782–1785.
[214] S.I. Borjesson, U.H. Englund, M.H. Asif, M. Willander, F. Elinder, Intracellular K+ concentration decrease is not obligatory for apoptosis, J. Biol. Chem. 286 (2011) 39823–39828.
[215] S. Bonnet, S.L. Archer, J. Allalunis-Turner, A. Haromy, C. Beaulieu, R. Thompson, C.T. Lee, G.D. Lopaschuk, L. Puttagunta, G. Harry, K. Hashimoto, C.J. Porter, M.A. Andrade, B. Thebaud, E.D. Michelakis, A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth, Cancer Cell 11 (2007) 37–51.
[216] J. Ousingsawat, M. Spitzner, S. Puntheeranurak, L. Terracciano, L. Tornillo, L. Bubendorf, K. Kunzelmann, R. Schreiber, Expression of voltage-gated potassium channels in human and mouse colonic carcinoma, Clin. Cancer Res. 13 (2007) 824–831.

[217] L. Leanza, P. O'Reilly, A. Doyle, E. Venturini, M. Zoratti, E. Szegezdi, I. Szabo, Correlation between potassium channel expression and sensitivity to drug-induced cell death in tumor cell lines, Curr. Pharm. Des. 20 (2014) 189–200.
[218] E. Fernandez-Segura, F.J. Canizares, M.A. Cubero, A. Warley, A. Campos, Changes in elemental content during apoptotic cell death studied by electron probe X-ray microanalysis, Exp. Cell Res. 253 (1999) 454–462.
[219] J.N. Skepper, I. Karydis, M.R. Garnett, L. Hegyi, S.J. Hardwick, A. Warley, M.J. Mitchinson, N.R. Cary, Changes in elemental concentrations are associated with early stages of apoptosis in human monocyte–macrophages exposed to oxidized low-density lipoprotein: an X-ray microanalytical study, J. Pathol. 188 (1999) 100–106.
[220] F. Arrebola, E. Fernandez-Segura, A. Campos, P.V. Crespo, J.N. Skepper, A. Warley, Changes in intracellular electrolyte concentrations during apoptosis induced by UV irradiation of human myeloblastic cells, Am. J. Physiol. Cell Physiol. 290 (2006) C638–649.
[221] F. Arrebola, S. Zabiti, F.J. Canizares, M.A. Cubero, P.V. Crespo, E. Fernandez-Segura, Changes in intracellular sodium, chlorine, and potassium concentrations in staurosporine-induced apoptosis, J. Cell. Physiol. 204 (2005) 500–507.
[222] C.D. Bortner, J.A. Cidlowski, Uncoupling cell shrinkage from apoptosis reveals that Na+ influx is required for volume loss during programmed cell death, J. Biol. Chem. 278 (2003) 39176–39184.
[223] C.D. Bortner, M. Gomez-Angelats, J.A. Cidlowski, Plasma membrane depolarization without repolarization is an early molecular event in anti-Fas-induced apoptosis, J. Biol. Chem. 276 (2001) 4304–4314.
[224] F. Nolte, O. Friedrich, M. Rojewski, R.H. Fink, H. Schrezenmeier, S. Korper, Depolarisation of the plasma membrane in the arsenic trioxide (As2O3)- and anti-CD95-induced apoptosis in myeloid cells, FEBS Lett. 578 (2004) 85–89.
[225] M.P. Courageot, S. Lepine, M. Hours, F. Giraud, J.C. Sulpice, Involvement of sodium in early phosphatidylserine exposure and phospholipid scrambling induced by P2X7 purinoceptor activation in thymocytes, J. Biol. Chem. 279 (2004) 21815–21823.
[226] J.L. Sui, J. Petit-Jacques, D.E. Logothetis, Activation of the atrial KACh channel by the betagamma subunits of G proteins or intracellular Na+ ions depends on the presence of phosphatidylinositol phosphates, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 1307–1312.
[227] I. Rishal, T. Keren-Raifman, D. Yakubovich, T. Ivanina, C.W. Dessauer, V.Z. Slepak, N. Dascal, Na+ promotes the dissociation between Galpha GDP and Gbeta gamma, activating G protein-gated K+ channels, J. Biol. Chem. 278 (2003) 3840–3845.
[228] M. Cochet-Bissuel, P. Lory, A. Monteil, The sodium leak channel, NALCN, in health and disease, Front. Cell. Neurosci. 8 (2014) 132.
[229] S. Kellenberger, L. Schild, Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure, Physiol. Rev. 82 (2002) 735–767.
[230] J.A. Wemmie, R.J. Taugher, C.J. Kreple, Acid-sensing ion channels in pain and disease, Nat. Rev. Neurosci. 14 (2013) 461–471.
[231] F.H. Yu, W.A. Catterall, Overview of the voltage-gated sodium channel family, Genome Biol. 4 (2003) 207.
[232] K.J. Banasiak, O. Burenkova, G.G. Haddad, Activation of voltage-sensitive sodium channels during oxygen deprivation leads to apoptotic neuronal death, Neuroscience 126 (2004) 31–44.
[233] J. Jordan, M.F. Galindo, C. Gonzalez-Garcia, V. Cena, Role and regulation of p53 in depolarization-induced neuronal death, Neuroscience 122 (2003) 707–715.
[234] J.K. Callaway, P.M. Beart, B. Jarrott, S.F. Giardina, Incorporation of sodium channel blocking and free radical scavenging activities into a single drug, AM-36, results in profound inhibition of neuronal apoptosis, Br. J. Pharmacol. 132 (2001) 1691–1698.
[235] C. Bohmer, C.A. Wagner, S. Beck, I. Moschen, J. Melzig, A. Werner, J.T. Lin, F. Lang, F. Wehner, The shrinkage-activated Na(+) conductance of rat hepatocytes and its possible correlation to rENaC, Cell. Physiol. Biochem. 10 (2000) 187–194.
[236] W. Hu, F.H. Chen, F.L. Yuan, T.Y. Zhang, F.R. Wu, C. Rong, S. Jiang, J. Tang, C.C. Zhang, M.Y. Lin, Blockade of acid-sensing ion channels protects articular chondrocytes from acid-induced apoptotic injury, Inflamm. Res. 61 (2012) 327–335.
[237] C. Rong, F.H. Chen, S. Jiang, W. Hu, F.R. Wu, T.Y. Chen, F.L. Yuan, Inhibition of acid-sensing ion channels by amiloride protects rat articular chondrocytes from acid-induced apoptosis via a mitochondrial-mediated pathway, Cell Biol. Int. 36 (2012) 635–641.
[238] Z.G. Xiong, X.M. Zhu, X.P. Chu, M. Minami, J. Hey, W.L. Wei, J.F. MacDonald, J.A. Wemmie, M.P. Price, M.J. Welsh, R.P. Simon, Neuroprotection in ischemia: blocking calcium-permeable acid-sensing ion channels, Cell 118 (2004) 687–698.
[239] O. Yermolaieva, A.S. Leonard, M.K. Schnizler, F.M. Abboud, M.J. Welsh, Extracellular acidosis increases neuronal cell calcium by activating acid-sensing ion channel 1a, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6752–6757.
[240] S.P. Fraser, I. Ozerlat-Gunduz, W.J. Brackenbury, E.M. Fitzgerald, T.M. Campbell, R.C. Coombes, M.B. Djamgoz, Regulation of voltage-gated sodium channel expression in cancer: hormones, growth factors and auto-regulation, Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (2014) 20130105.
[241] W.J. Brackenbury, A.M. Chioni, J.K. Diss, M.B. Djamgoz, The neonatal splice variant of Nav1.5 potentiates in vitro invasive behaviour of MDA-MB-231 human breast cancer cells, Breast Cancer Res. Treat. 101 (2007) 149–160.
[242] J.K. Diss, D. Stewart, F. Pani, C.S. Foster, M.M. Walker, A. Patel, M.B. Djamgoz, A potential novel marker for human prostate cancer: voltage-gated sodium channel expression in vivo, Prostate Cancer Prostatic Dis. 8 (2005) 266–273.
[243] E. Maeno, Y. Ishizaki, T. Kanaseki, A. Hazama, Y. Okada, Normotonic cell shrinkage because of disordered volume regulation is an early prerequisite to apoptosis, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 9487–9492.
[244] L. Wei, A.Y. Xiao, C. Jin, A. Yang, Z.Y. Lu, S.P. Yu, Effects of chloride and potassium channel blockers on apoptotic cell shrinkage and apoptosis in cortical neurons, Pflugers Arch. 448 (2004) 325–334.
[245] Y. Okada, T. Shimizu, E. Maeno, S. Tanabe, X. Wang, N. Takahashi, Volume-sensitive chloride channels involved in apoptotic volume decrease and cell death, J. Membr. Biol. 209 (2006) 21–29.
[246] I. Szabo, A. Lepple-Wienhues, K.N. Kaba, M. Zoratti, E. Gulbins, F. Lang, Tyrosine kinase-dependent activation of a chloride channel in CD95-induced apoptosis in T lymphocytes, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 6169–6174.
[247] B. Nilius, G. Droogmans, Amazing chloride channels: an overview, Acta Physiol. Scand. 177 (2003) 119–147.
[248] C. Duran, C.H. Thompson, Q. Xiao, H.C. Hartzell, Chloride channels: often enigmatic, rarely predictable, Annu. Rev. Physiol. 72 (2010) 95–121.
[249] J. Eggermont, D. Trouet, I. Carton, B. Nilius, Cellular function and control of volume-regulated anion channels, Cell Biochem. Biophys. 35 (2001) 263–274.
[250] T. Shimizu, T. Numata, Y. Okada, A role of reactive oxygen species in apoptotic activation of volume-sensitive Cl(−) channel, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6770–6773.
[251] M.V. Zamaraeva, R.Z. Sabirov, E. Maeno, Y. Ando-Akatsuka, S.V. Bessonova, Y. Okada, Cells die with increased cytosolic ATP during apoptosis: a bioluminescence study with intracellular luciferase, Cell Death Differ. 12 (2005) 1390–1397.
[252] Y. Okada, E. Maeno, T. Shimizu, K. Dezaki, J. Wang, S. Morishima, Receptor-mediated control of regulatory volume decrease (RVD) and apoptotic volume decrease (AVD), J. Physiol. 532 (2001) 3–16.
[253] S. Hortelano, M. Zeini, A. Castrillo, A.M. Alvarez, L. Bosca, Induction of apoptosis by nitric oxide in macrophages is independent of apoptotic volume decrease, Cell Death Differ. 9 (2002) 643–650.
[254] T. Ise, T. Shimizu, E.L. Lee, H. Inoue, K. Kohno, Y. Okada, Roles of volume-sensitive Cl^- channel in cisplatin-induced apoptosis in human epidermoid cancer cells, J. Membr. Biol. 205 (2005) 139–145.
[255] E.L. Lee, T. Shimizu, T. Ise, T. Numata, K. Kohno, Y. Okada, Impaired activity of volume-sensitive Cl^- channel is involved in cisplatin resistance of cancer cells, J. Cell. Physiol. 211 (2007) 513–521.
[256] X.J. Min, H. Li, S.C. Hou, W. He, J. Liu, B. Hu, J. Wang, Dysfunction of volume-sensitive chloride channels contributes to cisplatin resistance in human lung adenocarcinoma cells, Exp. Biol. Med. (Maywood) 236 (2011) 483–491.
[257] D. Duan, C. Winter, S. Cowley, J.R. Hume, B. Horowitz, Molecular identification of a volume-regulated chloride channel, Nature 390 (1997) 417–421.
[258] M. Hermoso, C.M. Satterwhite, Y.N. Andrade, J. Hidalgo, S.M. Wilson, B. Horowitz, J.R. Hume, ClC-3 is a fundamental molecular component of volume-sensitive outwardly rectifying Cl^- channels and volume regulation in HeLa cells and Xenopus laevis oocytes, J. Biol. Chem. 277 (2002) 40066–40074.
[259] L. Lemonnier, Y. Shuba, A. Crepin, M. Roudbaraki, C. Slomianny, B. Mauroy, B. Nilius, N. Prevarskaya, R. Skryma, Bcl-2-dependent modulation of swelling-activated Cl^- current and ClC-3 expression in human prostate cancer epithelial cells, Cancer Res. 64 (2004) 4841–4848.
[260] L. Lemonnier, R. Lazarenko, Y. Shuba, S. Thebault, M. Roudbaraki, G. Lepage, N. Prevarskaya, R. Skryma, Alterations in the regulatory volume decrease (RVD) and swelling-activated Cl^-- current associated with neuroendocrine differentiation of prostate cancer epithelial cells, Endocr. Relat. Cancer 12 (2005) 335–349.
[261] G. Cheng, Z. Shao, B. Chaudhari, D.K. Agrawal, Involvement of chloride channels in TGF-beta1-induced apoptosis of human bronchial epithelial cells, Am. J. Physiol. Lung Cell. Mol. Physiol. 293 (2007) L1339–1347.
[262] K.H. Weylandt, M. Nebrig, N. Jansen-Rosseck, J.S. Amey, D. Carmena, B. Wiedenmann, C.F. Higgins, A. Sardini, ClC-3 expression enhances etoposide resistance by increasing acidification of the late endocytic compartment, Mol. Cancer Ther. 6 (2007) 979–986.
[263] S.M. Stobrawa, T. Breiderhoff, S. Takamori, D. Engel, M. Schweizer, A.A. Zdebik, M.R. Bosl, K. Ruether, H. Jahn, A. Draguhn, R. Jahn, T.J. Jentsch, Disruption of ClC-3, a chloride channel expressed on synaptic vesicles, leads to a loss of the hippocampus, Neuron 29 (2001) 185–196.
[264] J. Arreola, T. Begenisich, K. Nehrke, H.V. Nguyen, K. Park, L. Richardson, B. Yang, B.C. Schutte, F.S. Lamb, J.E. Melvin, Secretion and cell volume regulation by salivary acinar cells from mice lacking expression of the Clcn3 Cl^- channel gene, J. Physiol. 545 (2002) 207–216.
[265] W. Gong, H. Xu, T. Shimizu, S. Morishima, S. Tanabe, T. Tachibe, S. Uchida, S. Sasaki, Y. Okada, ClC-3-independent, PKC-dependent activity of volume-sensitive Cl channel in mouse ventricular cardiomyocytes, Cell. Physiol. Biochem. 14 (2004) 213–224.
[266] J.R. Martins, D. Faria, P. Kongsuphol, B. Reisch, R. Schreiber, K. Kunzelmann, Anoctamin 6 is an essential component of the outwardly rectifying chloride channel, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 18168–18172.
[267] T. Shimizu, T. Iehara, K. Sato, T. Fujii, H. Sakai, Y. Okada, TMEM16F is a component of a Ca2 + -activated Cl^- channel but not a volume-sensitive outwardly rectifying Cl^- channel, Am. J. Physiol. Cell Physiol. 304 (2013) C748–759.
[268] C.A. Juul, S. Grubb, K.A. Poulsen, T. Kyed, N. Hashem, I.H. Lambert, E.H. Larsen, E.K. Hoffmann, Anoctamin 6 differs from VRAC and VSOAC but is involved in apoptosis and supports volume regulation in the presence of Ca, Pflugers Arch. 466 (2014) 1899–1910.
[269] J. Suzuki, M. Umeda, P.J. Sims, S. Nagata, Calcium-dependent phospholipid scrambling by TMEM16F, Nature 468 (2010) 834–838.
[270] I. Rubera, C. Duranton, N. Melis, M. Cougnon, B. Mograbi, M. Tauc, Role of CFTR in oxidative stress and suicidal death of renal cells during cisplatin-induced nephrotoxicity, Cell Death Dis. 4 (2013) e817.
[271] H. Barriere, C. Poujeol, M. Tauc, J.M. Blasi, L. Counillon, P. Poujeol, CFTR modulates programmed cell death by decreasing intracellular pH in Chinese hamster lung fibroblasts, Am. J. Physiol. Cell Physiol. 281 (2001) C810–824.

[272] E. Fernandez-Salas, K.S. Suh, V.V. Speransky, W.L. Bowers, J.M. Levy, T. Adams, K.R. Pathak, L.E. Edwards, D.D. Hayes, C. Cheng, A.C. Steven, W.C. Weinberg, S.H. Yuspa, mtCLIC/CLIC4, an organellular chloride channel protein, is increased by DNA damage and participates in the apoptotic response to p53, Mol. Cell. Biol. 22 (2002) 3610–3620.
[273] K.S. Suh, M. Mutoh, K. Nagashima, E. Fernandez-Salas, L.E. Edwards, D.D. Hayes, J.M. Crutchley, K.G. Marin, R.A. Dumont, J.M. Levy, C. Cheng, S. Garfield, S.H. Yuspa, The organellular chloride channel protein CLIC4/mtCLIC translocates to the nucleus in response to cellular stress and accelerates apoptosis, J. Biol. Chem. 279 (2004) 4632–4641.
[274] K.S. Suh, M. Malik, A. Shukla, A. Ryscavage, L. Wright, K. Jividen, J.M. Crutchley, R.A. Dumont, E. Fernandez-Salas, J.D. Webster, R.M. Simpson, S.H. Yuspa, CLIC4 is a tumor suppressor for cutaneous squamous cell cancer, Carcinogenesis 33 (2012) 986–995.